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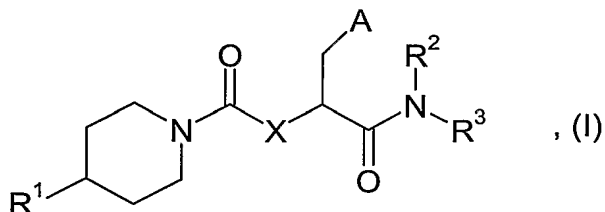
Veröffentlicht:

— mit internationalem Recherchenbericht  
— vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen

[Fortsetzung auf der nächsten Seite]

(54) Title: SELECTED CGRP-ANTAGONISTS, THEIR PREPARATION PROCESSES AND THEIR USE AS MEDICAMENTS

(54) Bezeichnung: AUSGEWÄHLTE CGRP-ANTAGONISTEN, VERFAHREN ZU DEREN HERSTELLUNG SOWIE DEREN VERWENDUNG ALS ARZNEIMITTEL



(57) Abstract: CGRP-antagonists are disclosed having the general formula (I), in which A, X and R<sup>1</sup>-R<sup>3</sup> have the definition given in claim 1, as well as their tautomers, diastereomers, enantiomers, hydrates, mixtures and salts, as well as their salt hydrates, in particular their physiologically compatible salts with inorganic or organic acids, medicaments containing these compounds, their use and their preparation processes.

(57) Zusammenfassung: Gegenstand der vorliegenden Erfindung sind die CGRP-Antagonisten der allgemeinen Formel (I) in der A, X und R<sup>1</sup> bis R<sup>3</sup> wie in Anspruch 1 definiert sind, deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren, diese Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer Herstellung.

WO 2005/100352 A1



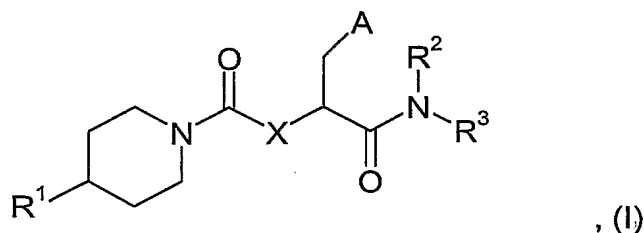
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*Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.*

## Ausgewählte CGRP-Antagonisten, Verfahren zu deren Herstellung sowie deren Verwendung als Arzneimittel

Gegenstand der vorliegenden Erfindung sind die CGRP-Antagonisten der allgemei-

5



deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren

10 Gemische und deren Salze sowie die Hydrate der Salze, insbesondere deren physio-

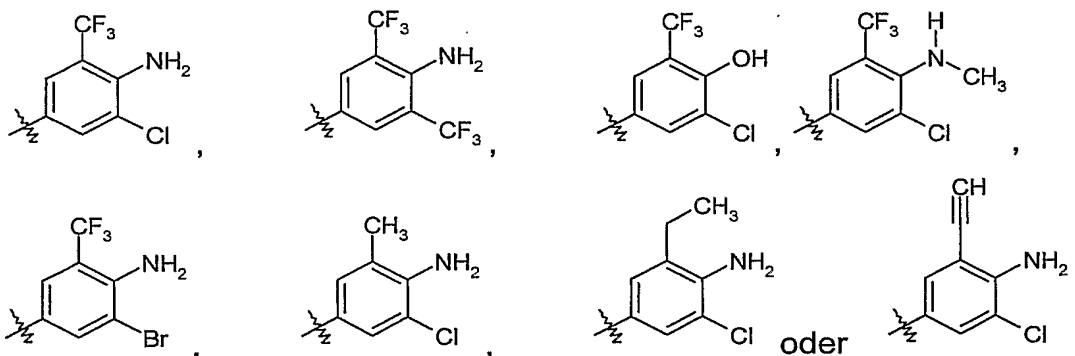
logisch verträgliche Salze mit anorganischen oder organischen Säuren, diese

Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer

Herstellung.

15 In der obigen allgemeinen Formel (I) bedeuten

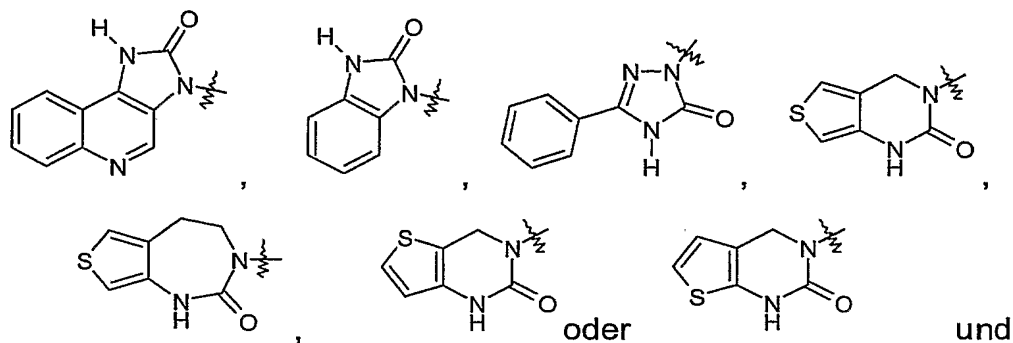
A einen Rest der Formel



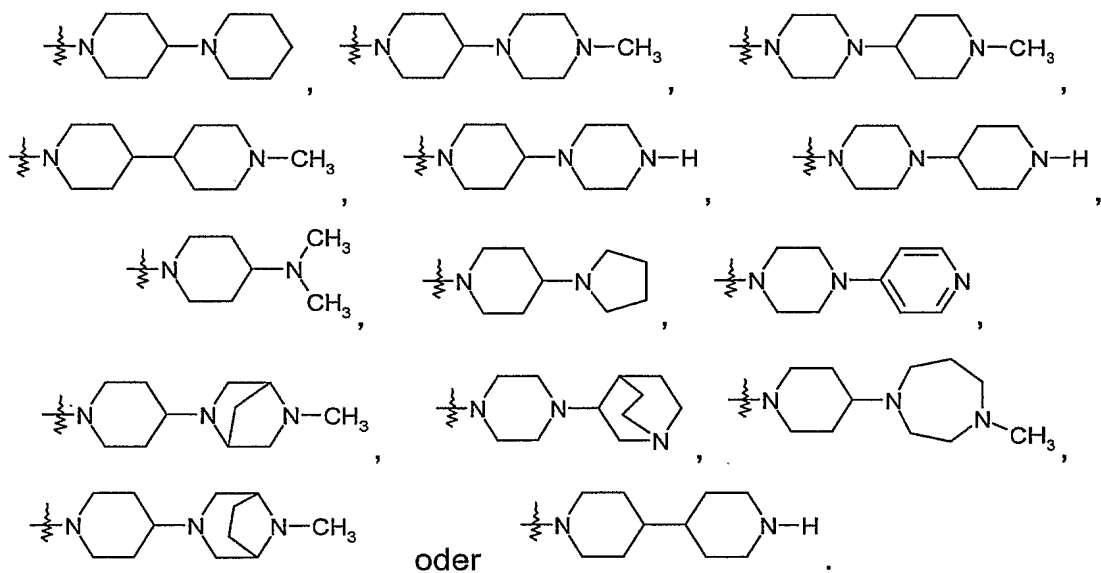
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X ein Sauerstoffatom, eine Methylen- oder NH-Gruppe,

R<sup>1</sup> einen Rest der Formel

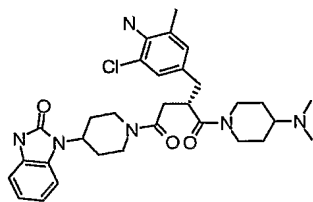


5 -NR<sup>2</sup>R<sup>3</sup> einen Rest der Formel

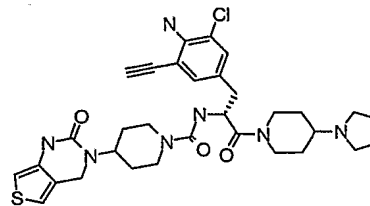


Besonders bevorzugte Verbindungen der obigen allgemeinen Formel (I) sind beispielsweise folgende:

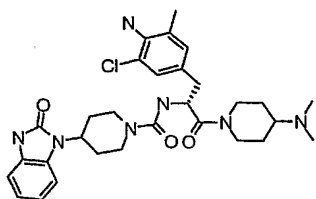
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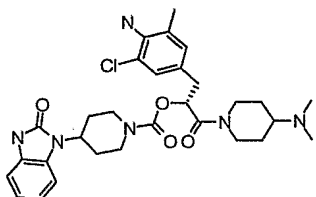
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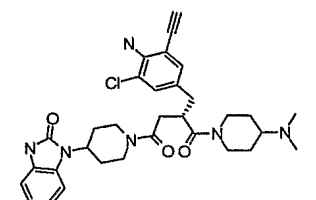
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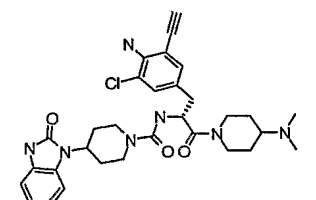
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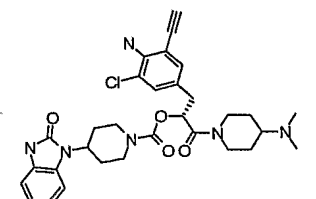
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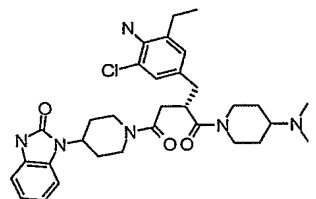
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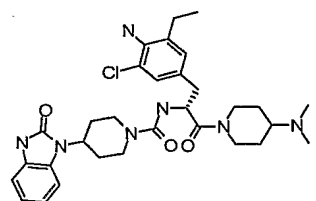
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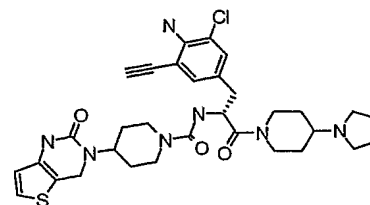
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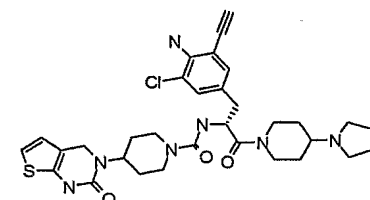
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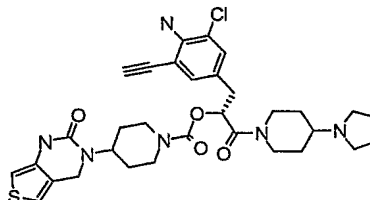
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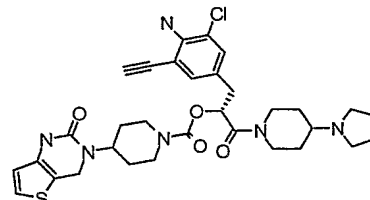
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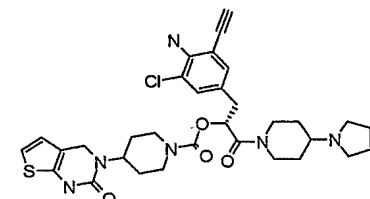
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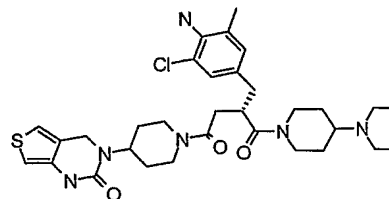
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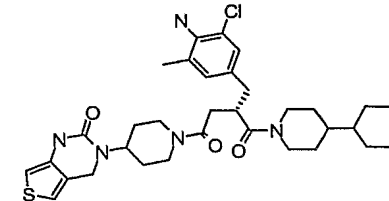
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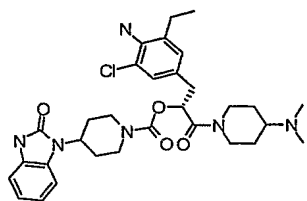
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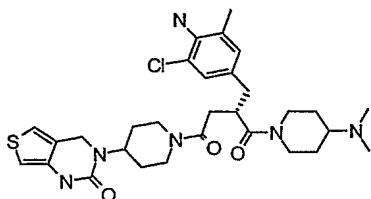
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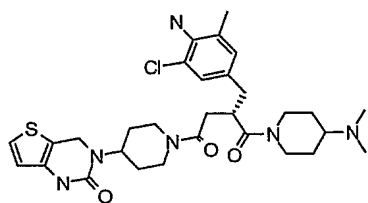
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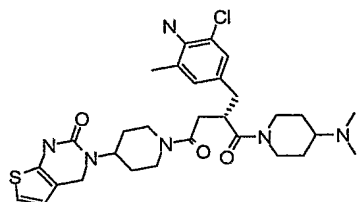
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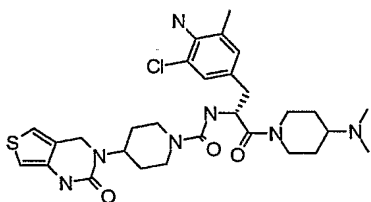
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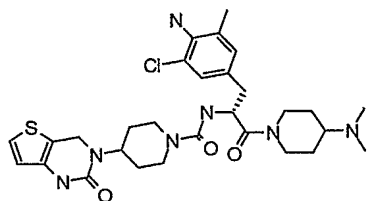
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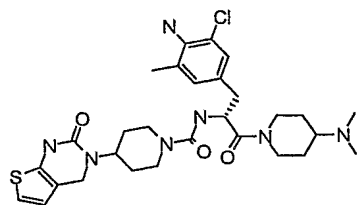
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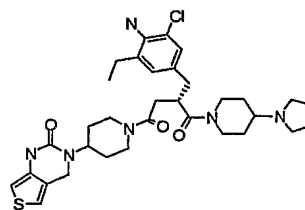
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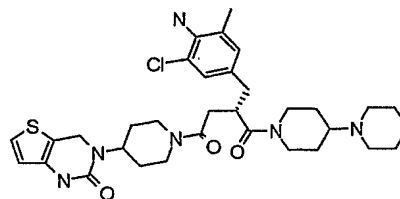
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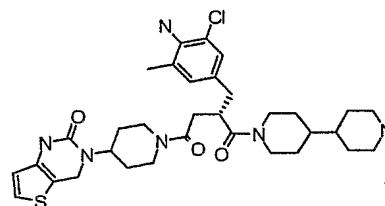
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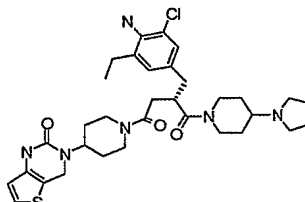
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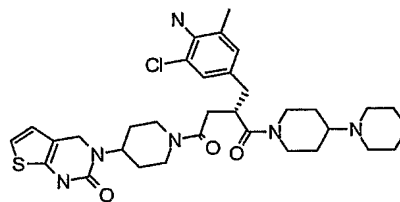
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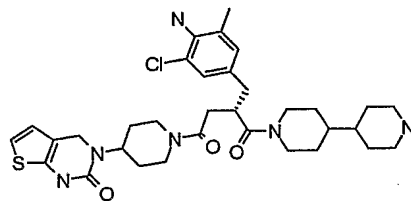
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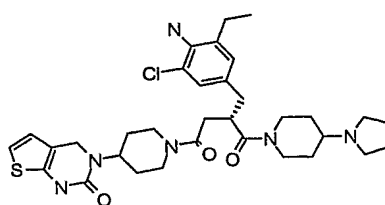
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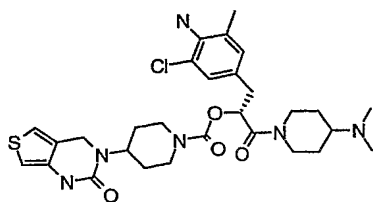
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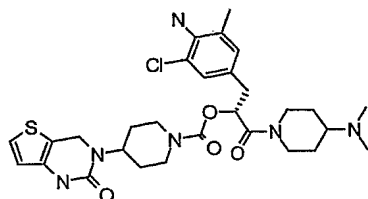
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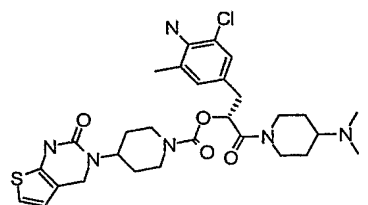
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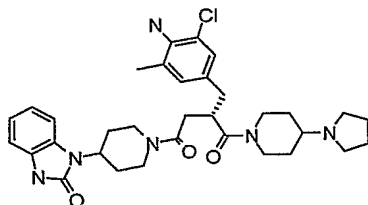
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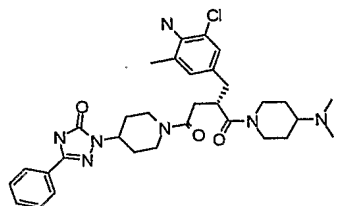
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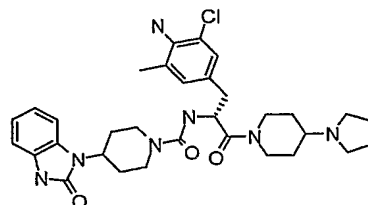
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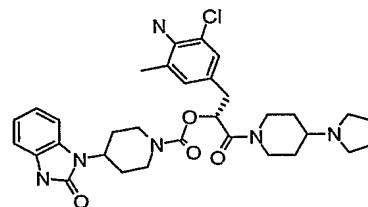
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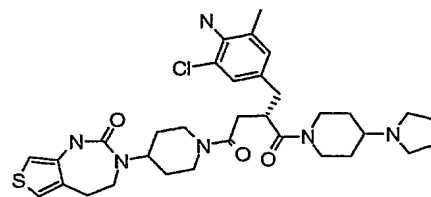
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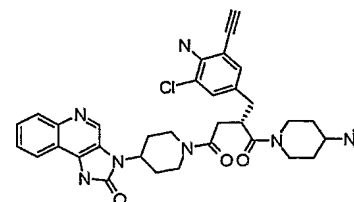
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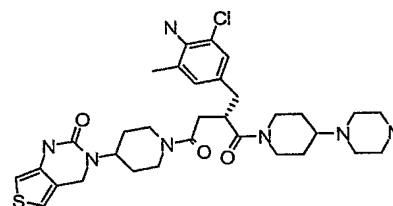
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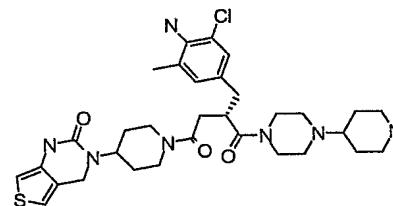
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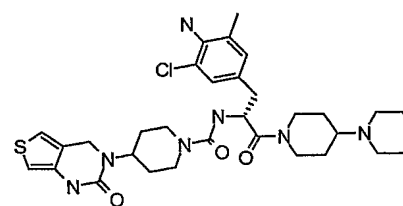
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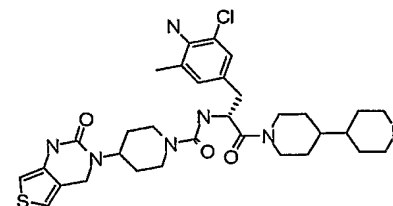
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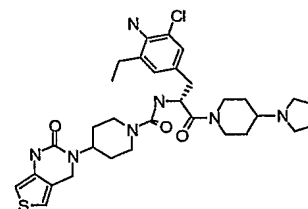
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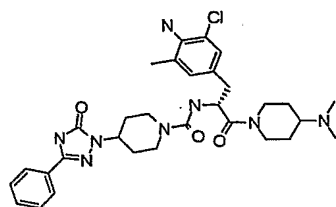
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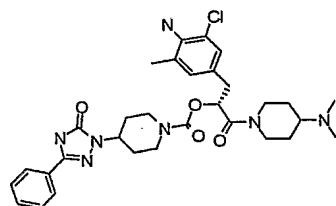
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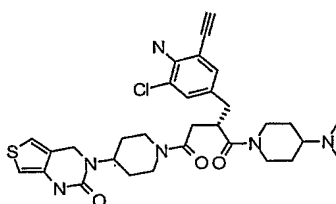
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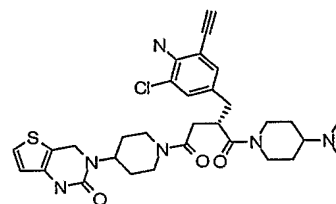
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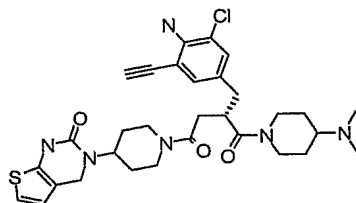
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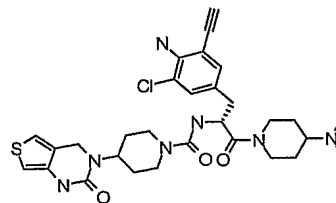
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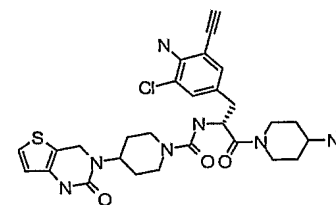
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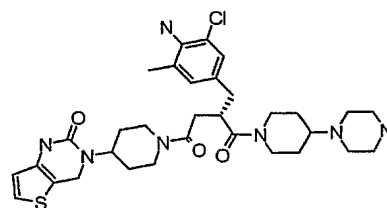
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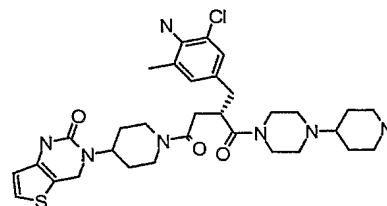
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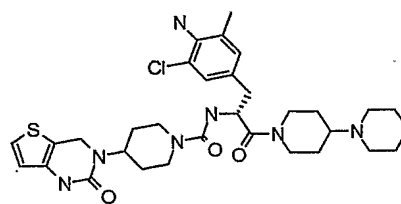
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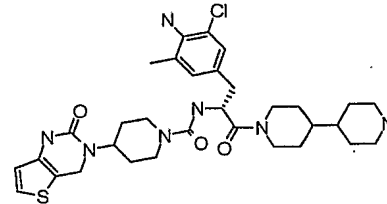
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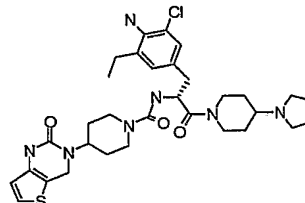
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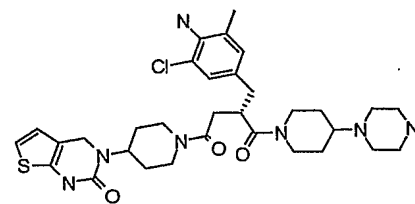
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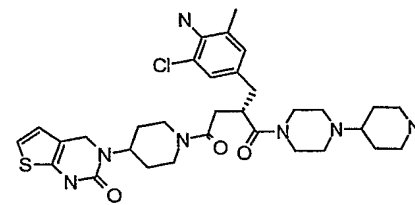
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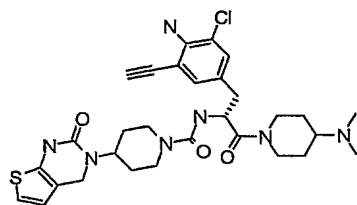
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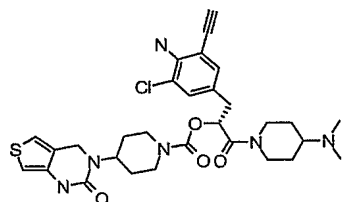
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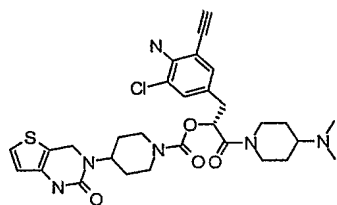
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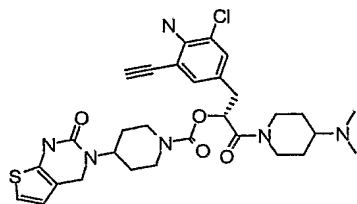
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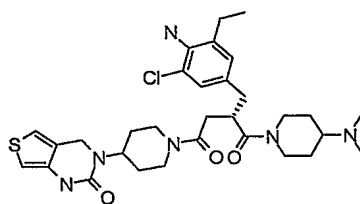
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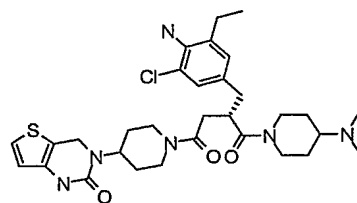
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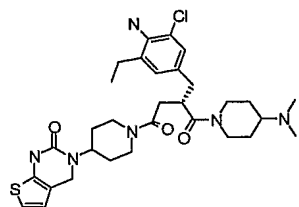
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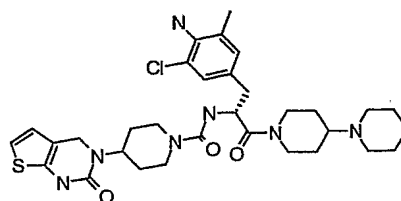
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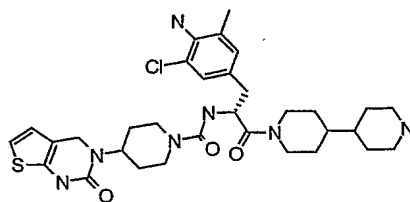
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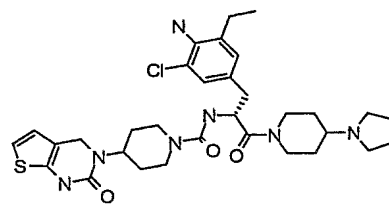
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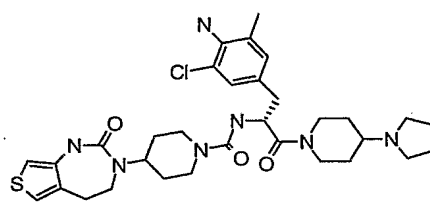
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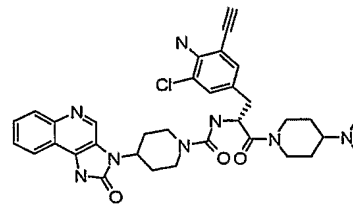
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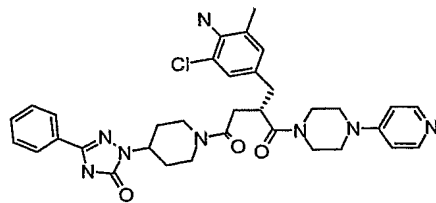
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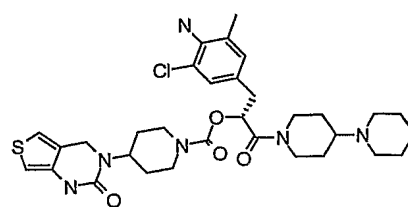
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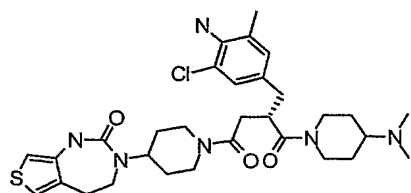
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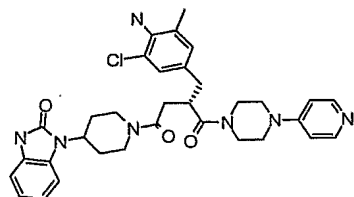
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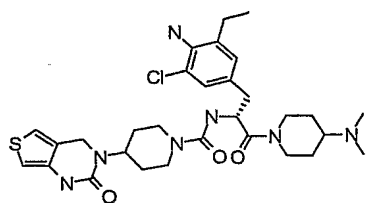
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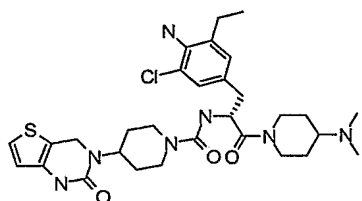
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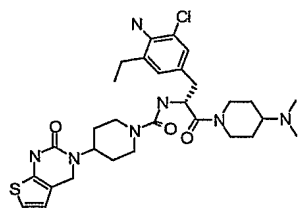
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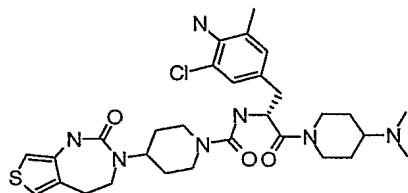
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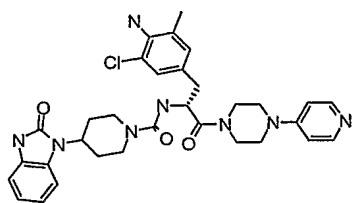
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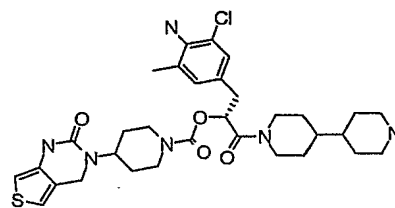
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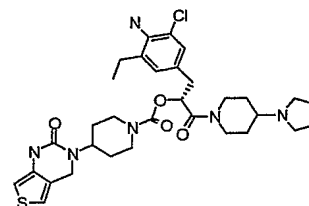
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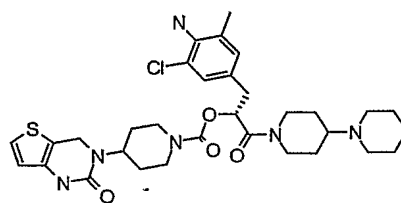
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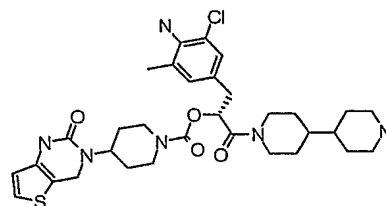
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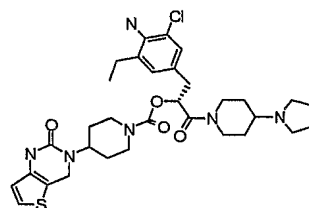
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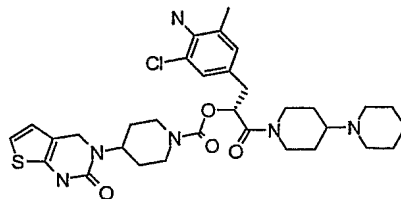
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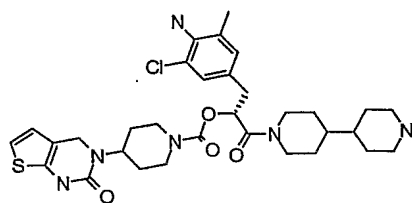
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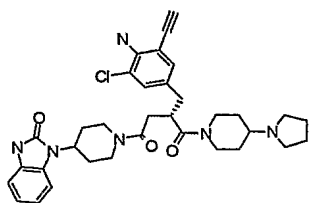
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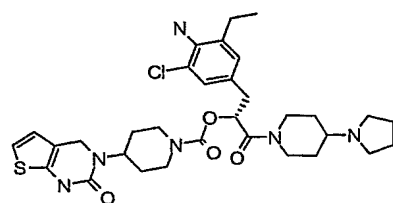
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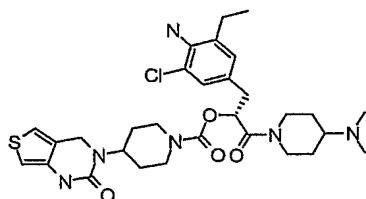
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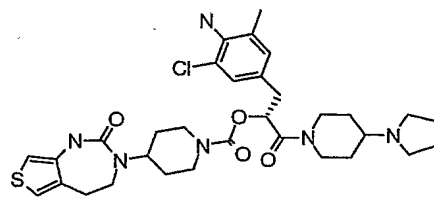
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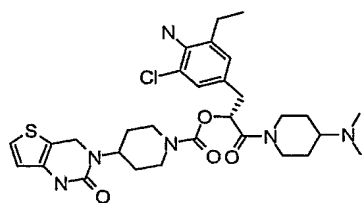
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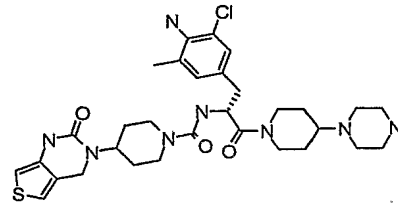
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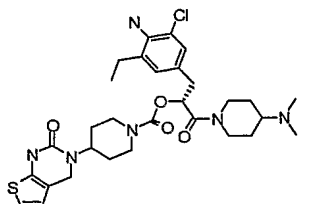
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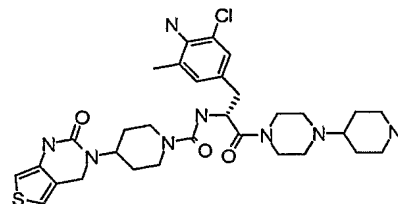
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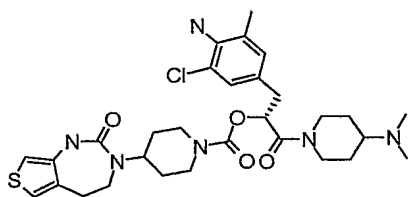
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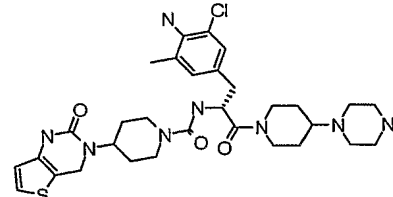
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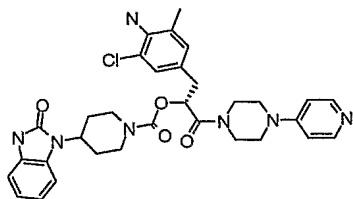
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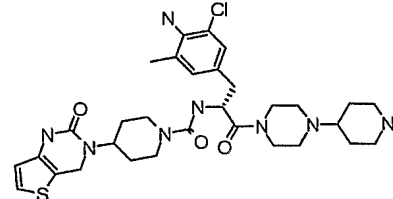
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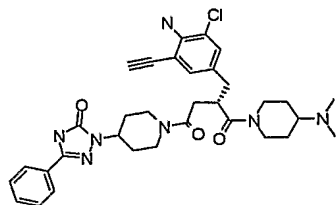
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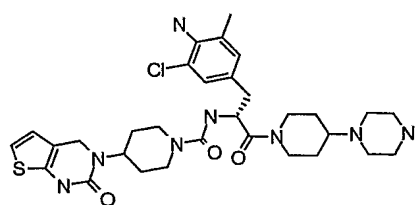
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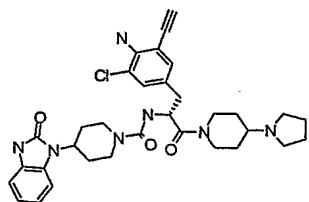
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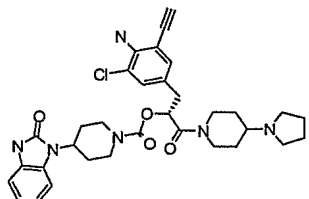
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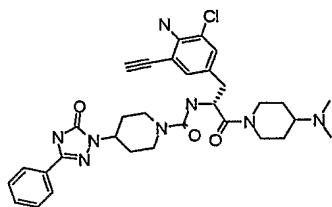
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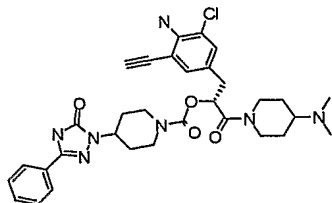
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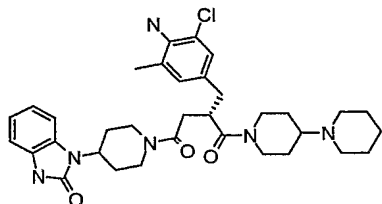
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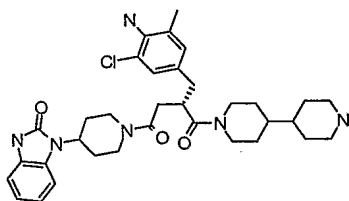
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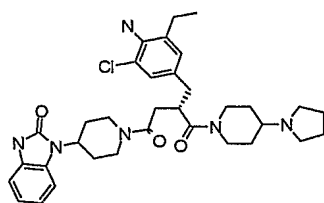
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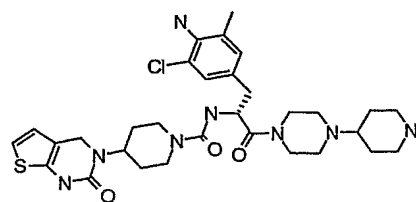
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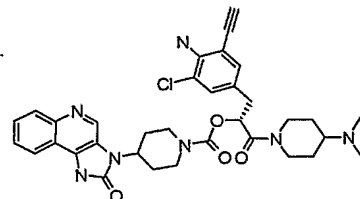
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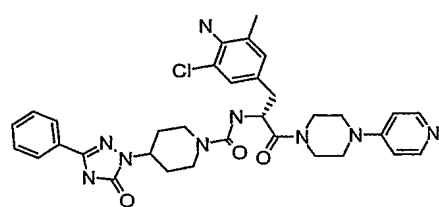
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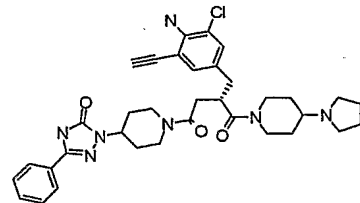
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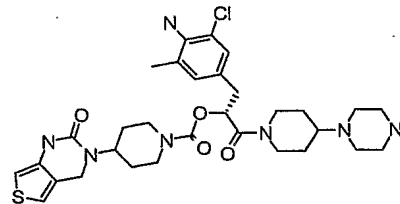
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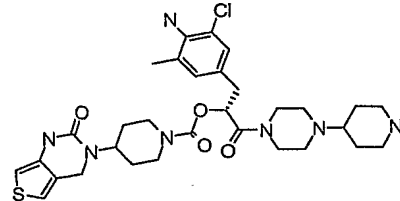
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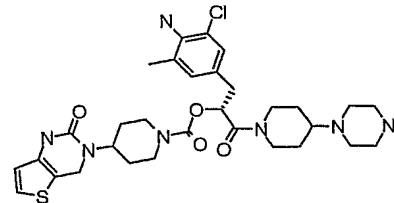
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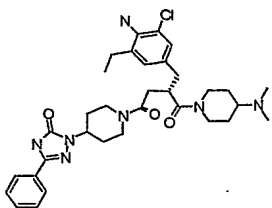
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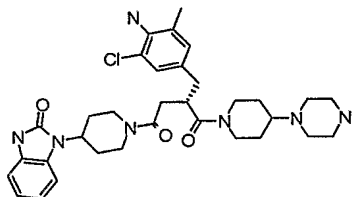
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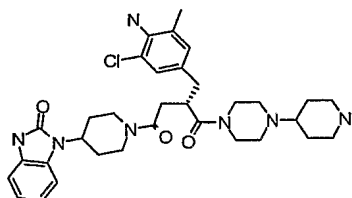
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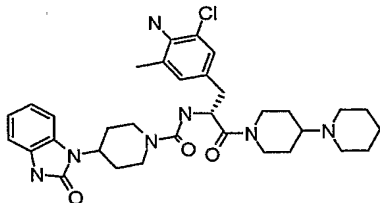
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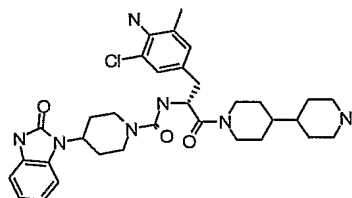
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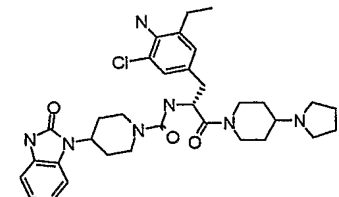
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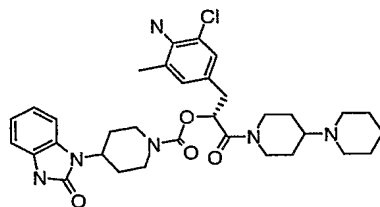
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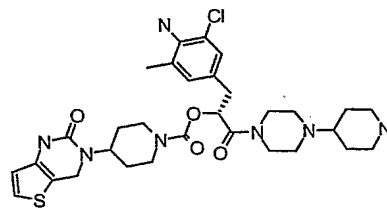
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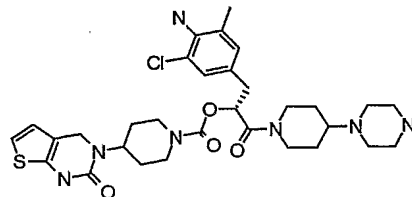
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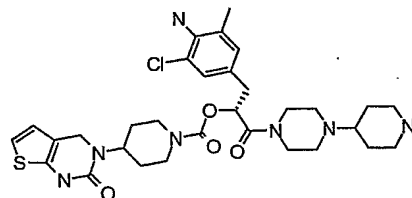
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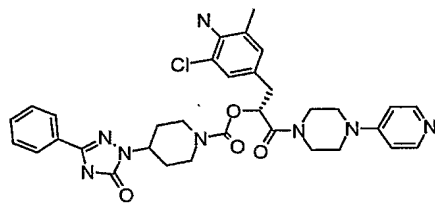
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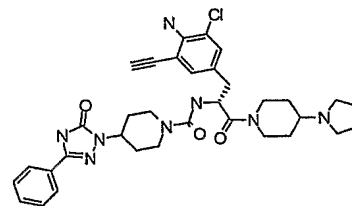
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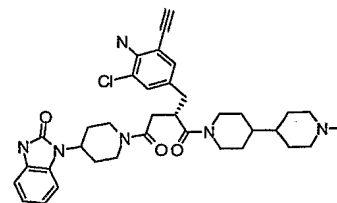
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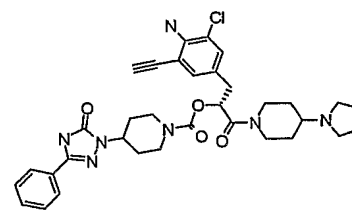
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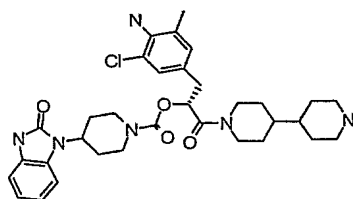
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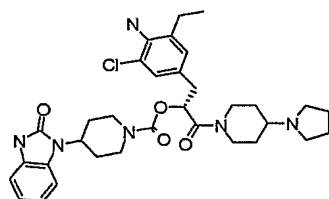
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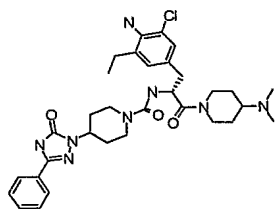
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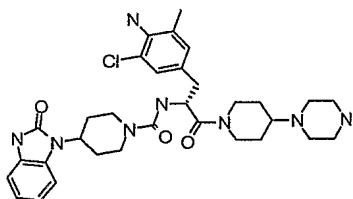
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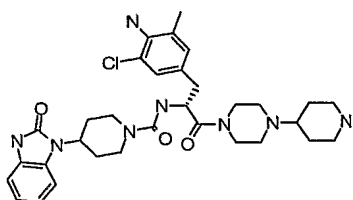
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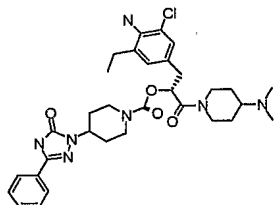
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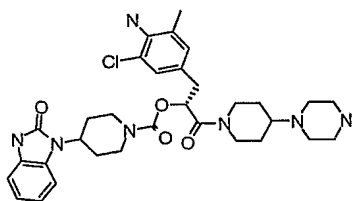
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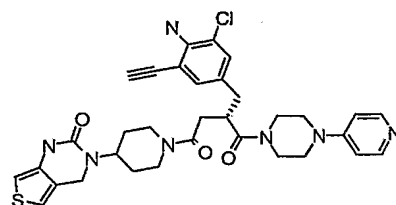
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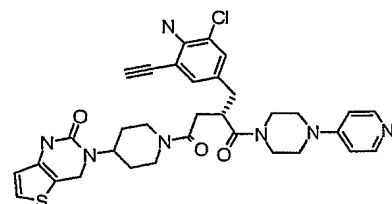
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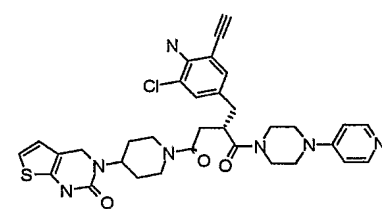
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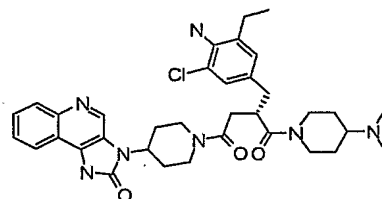
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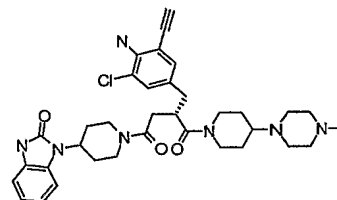
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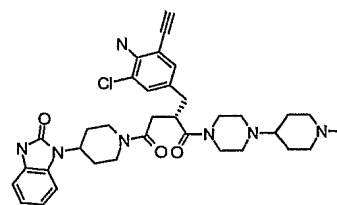
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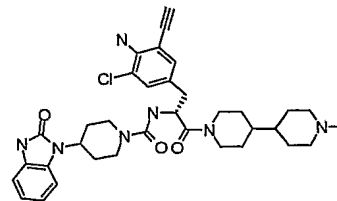
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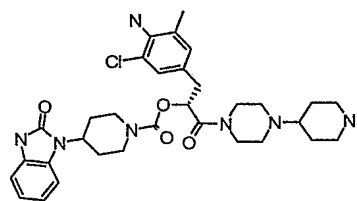
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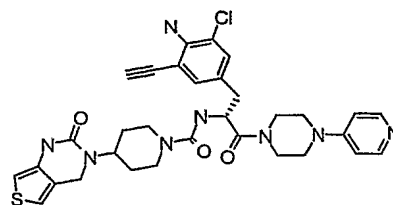
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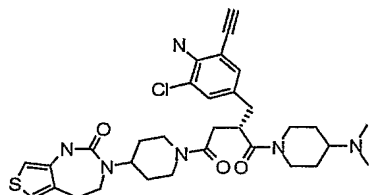
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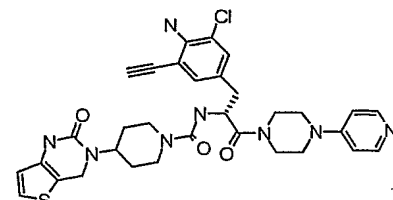
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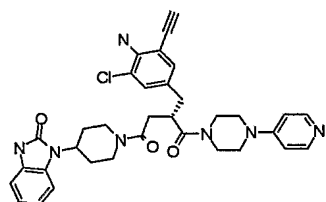
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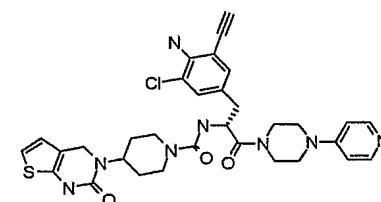
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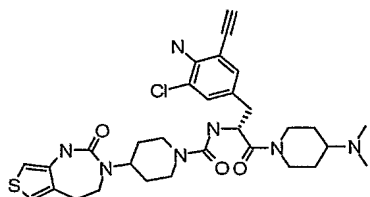
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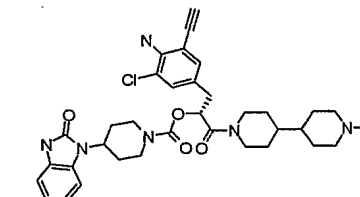
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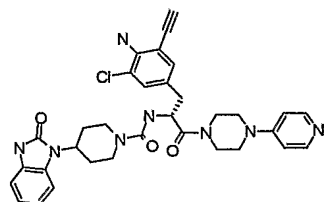
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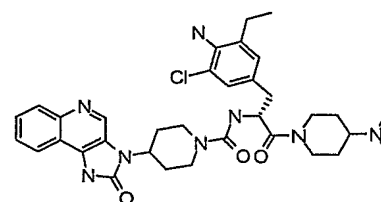
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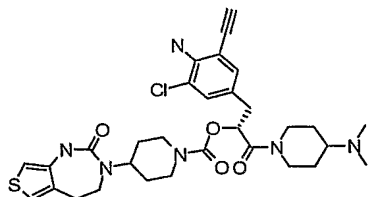
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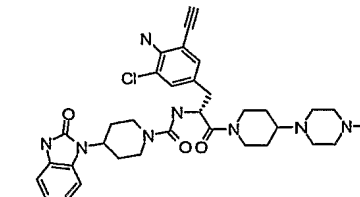
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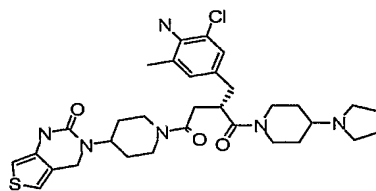
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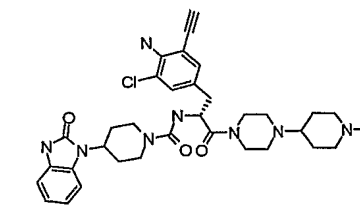
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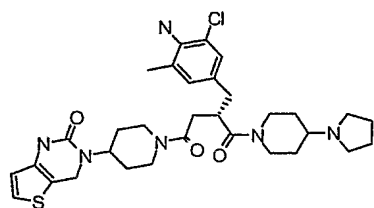
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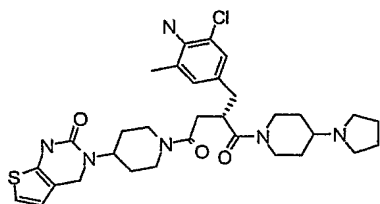
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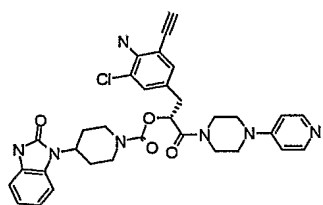
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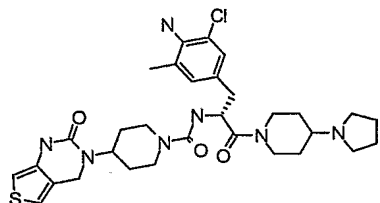
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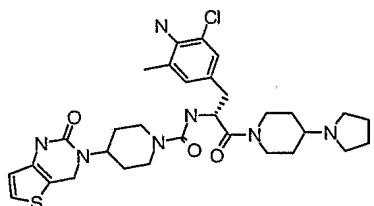
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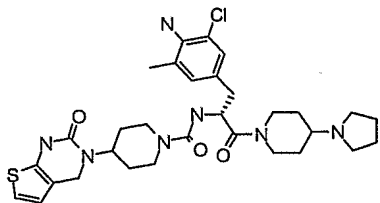
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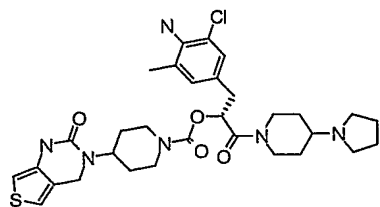
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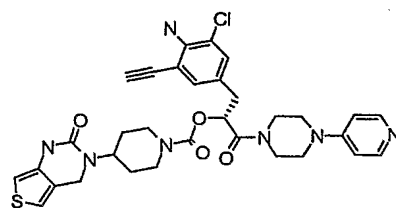
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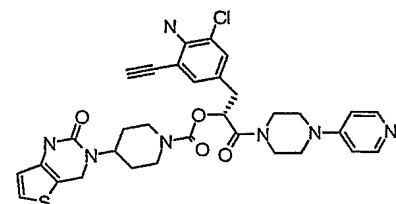
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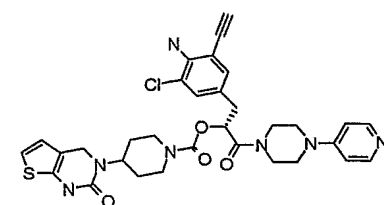
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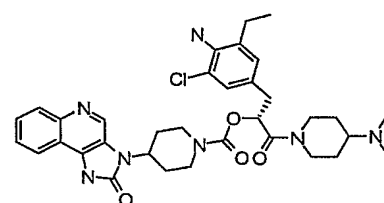
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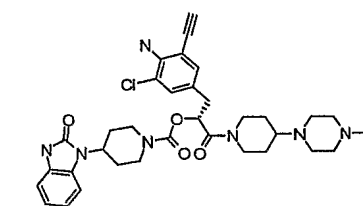
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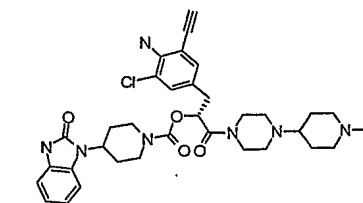
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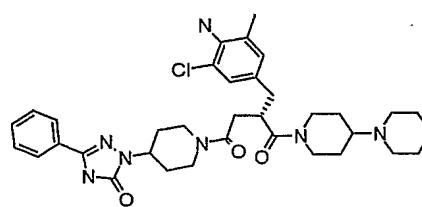
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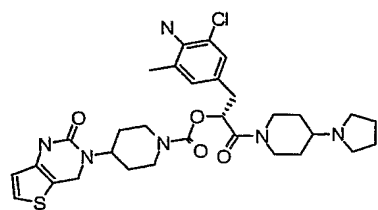
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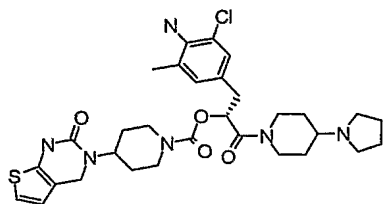
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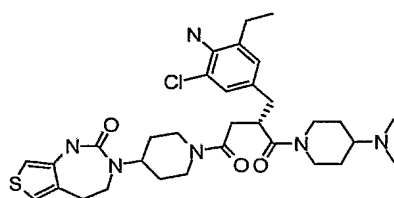
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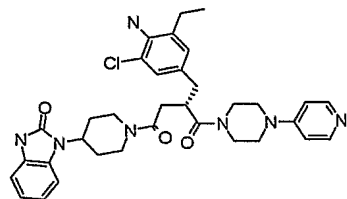
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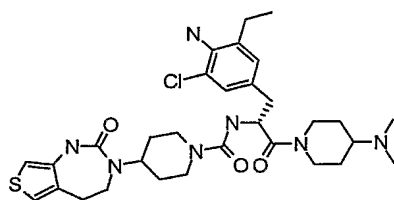
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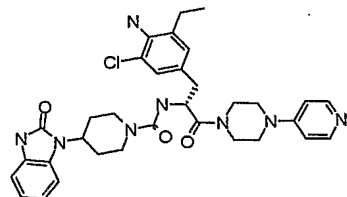
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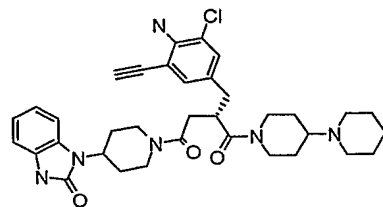
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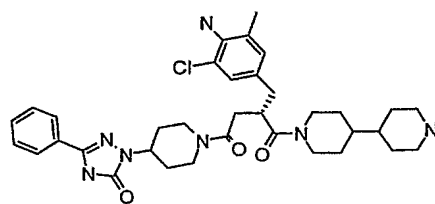
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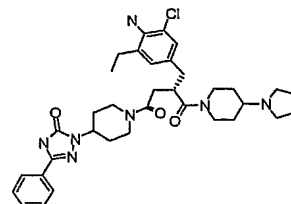
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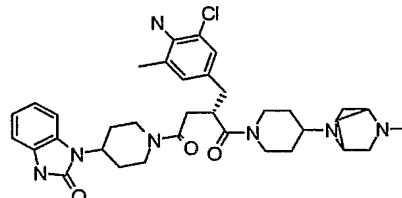
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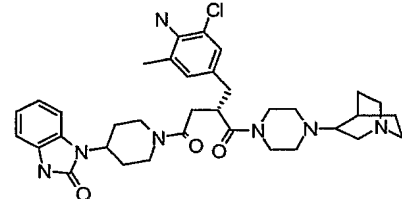
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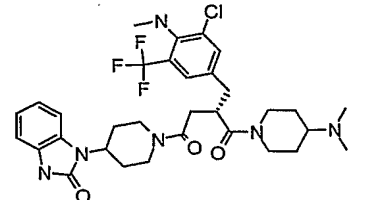
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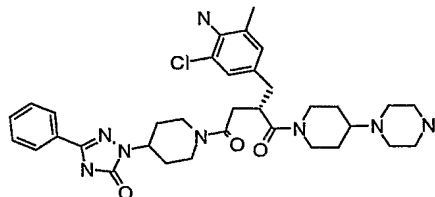
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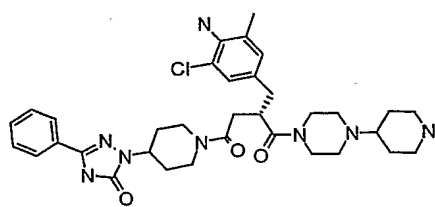
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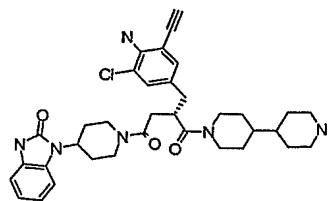
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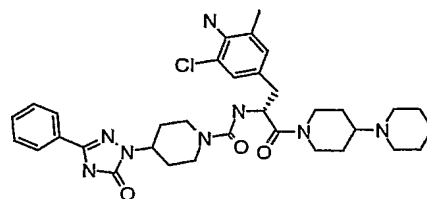
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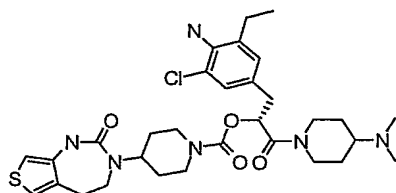
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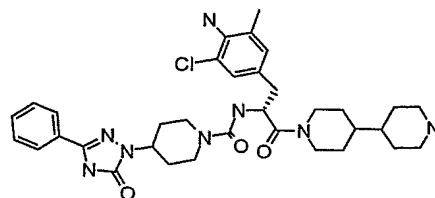
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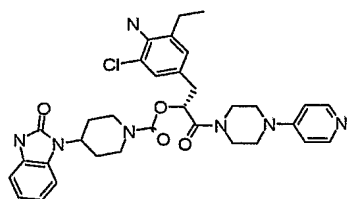
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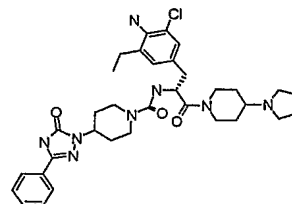
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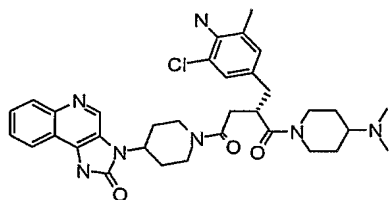
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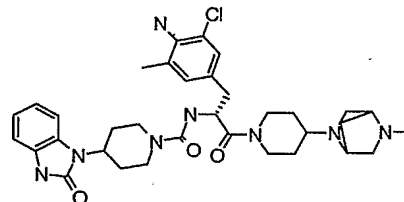
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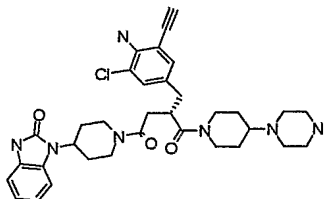
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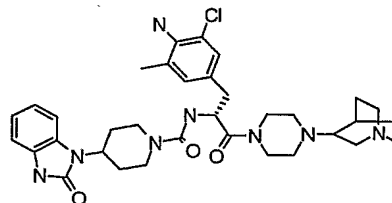
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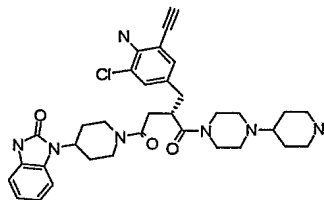
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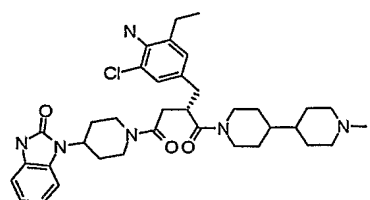
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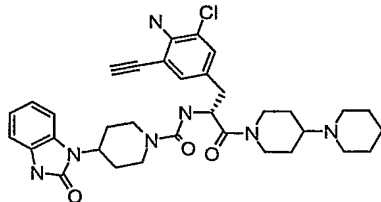
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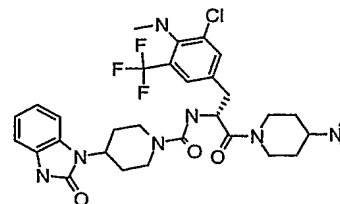
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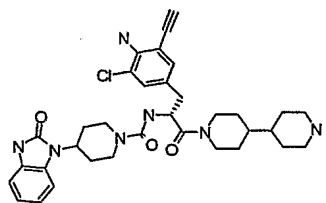
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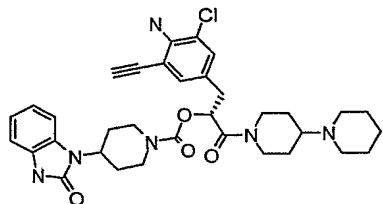
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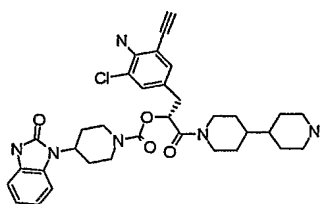
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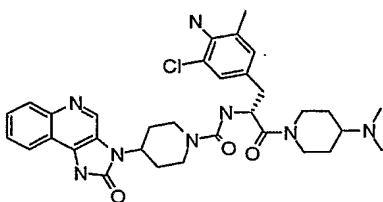
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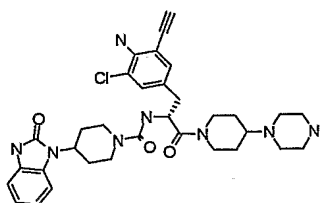
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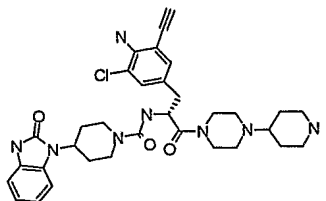
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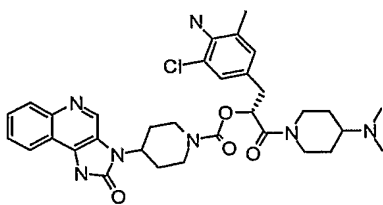
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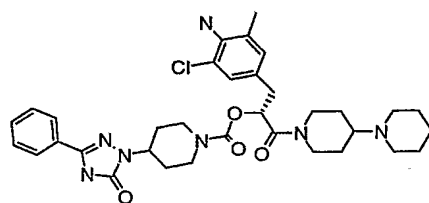
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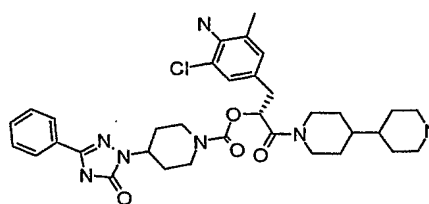
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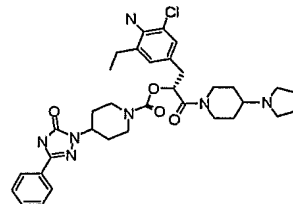
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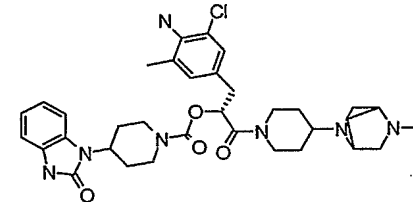
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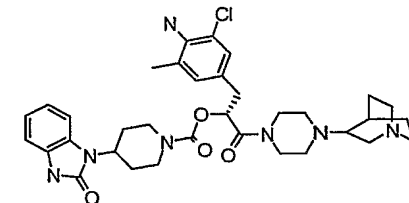
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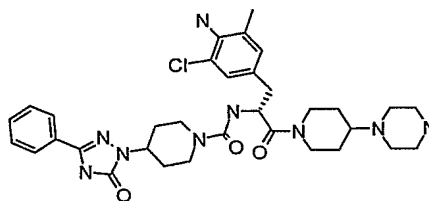
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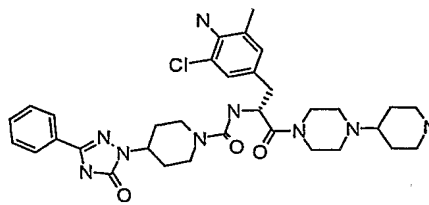
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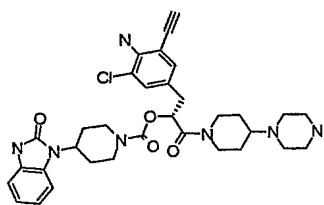
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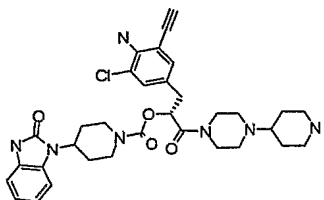
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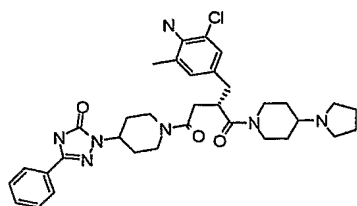
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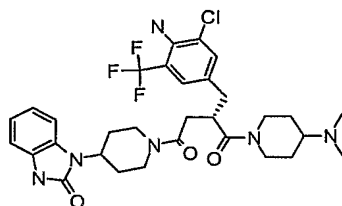
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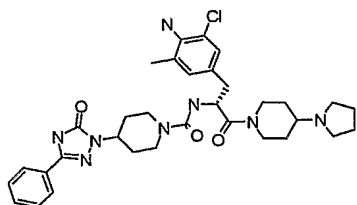
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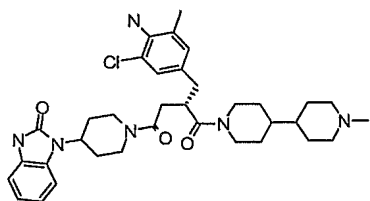
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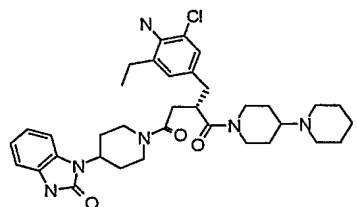
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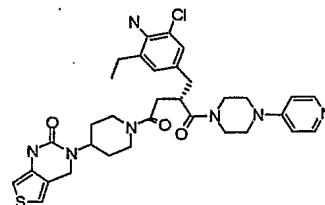
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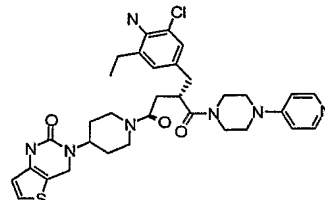
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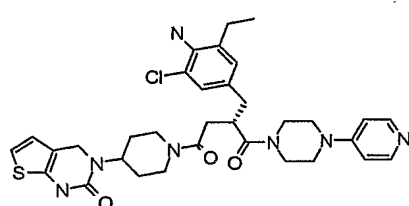
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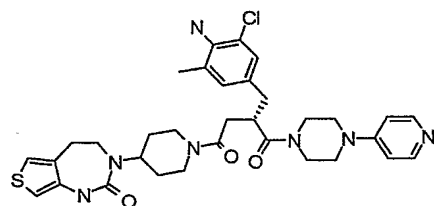
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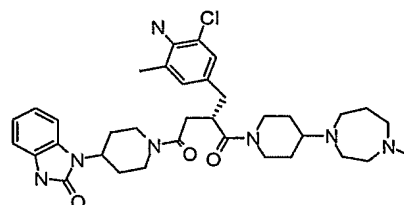
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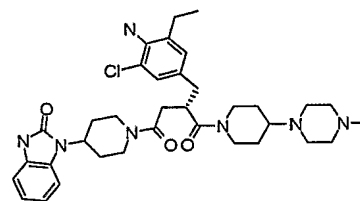
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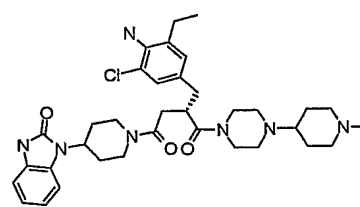
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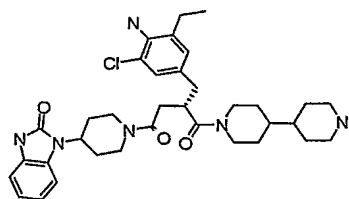
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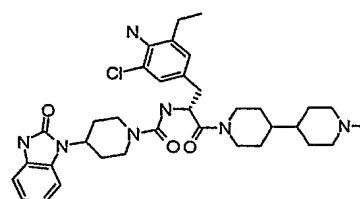
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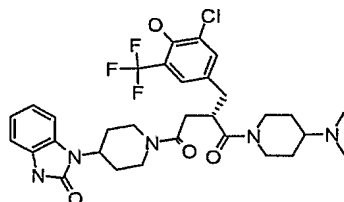
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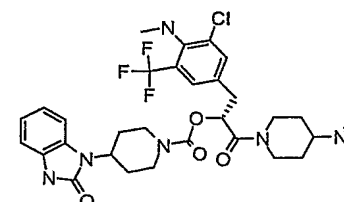
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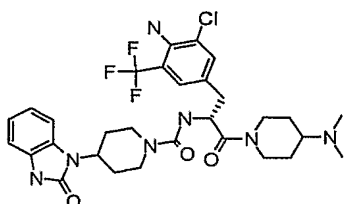
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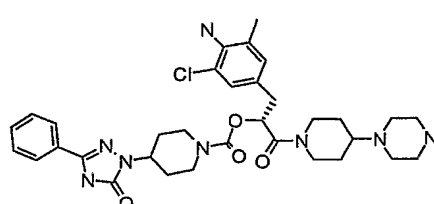
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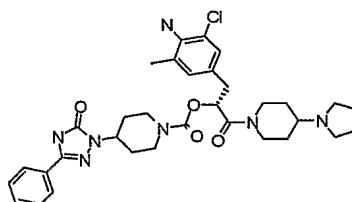
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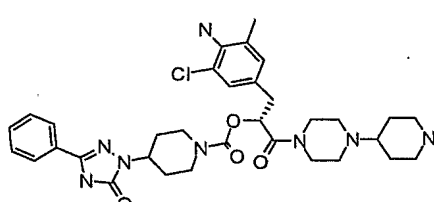
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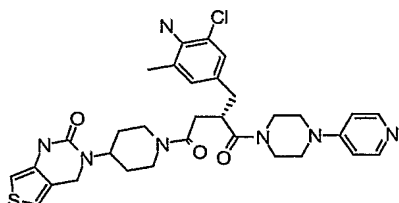
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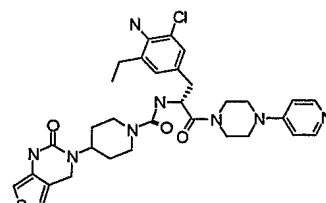
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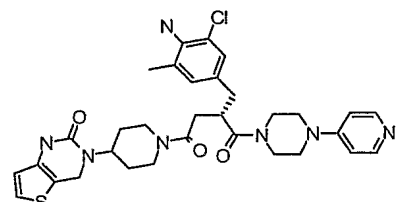
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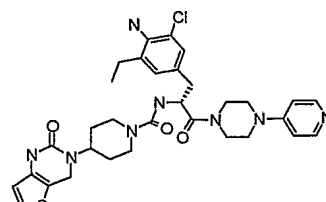
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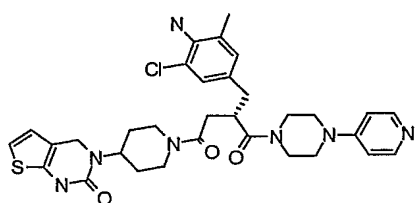
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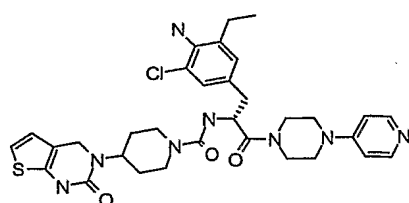
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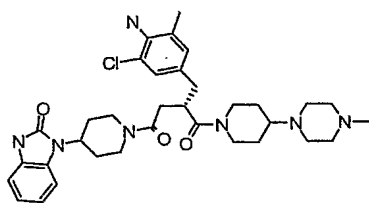
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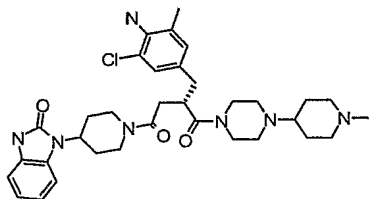
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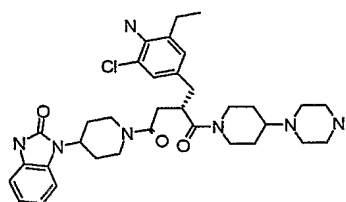
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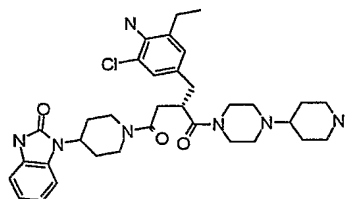
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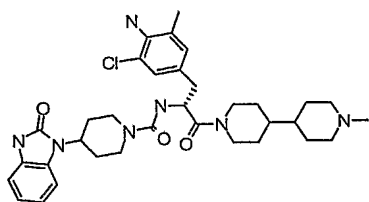
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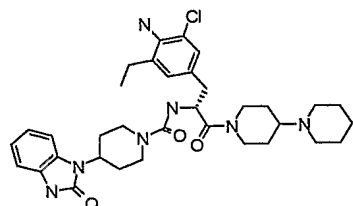
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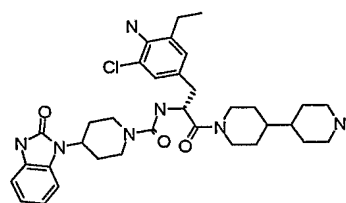
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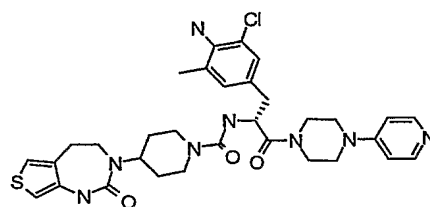
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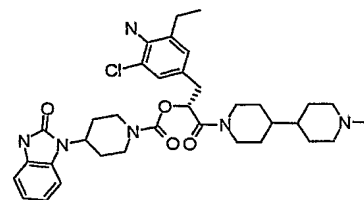
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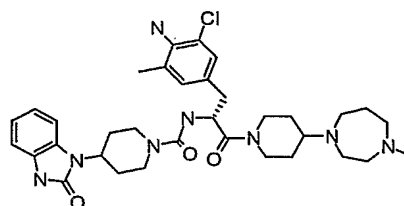
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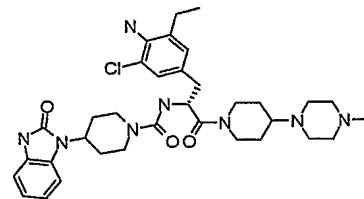
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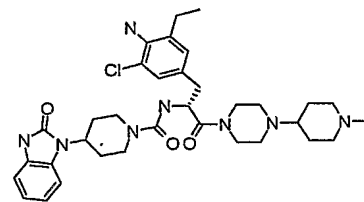
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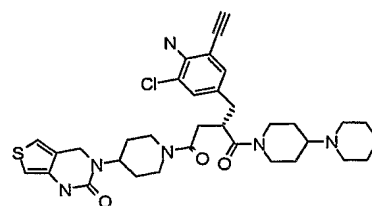
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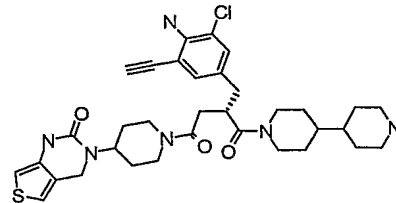
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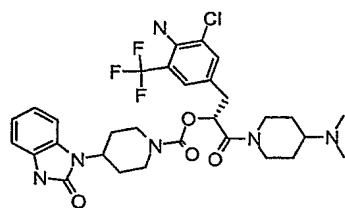
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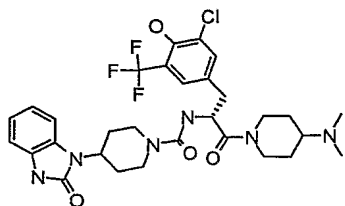
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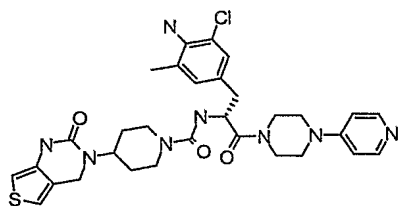
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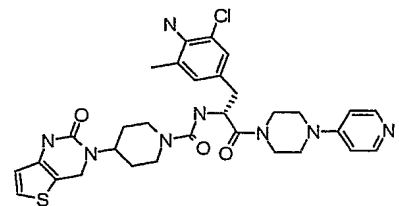
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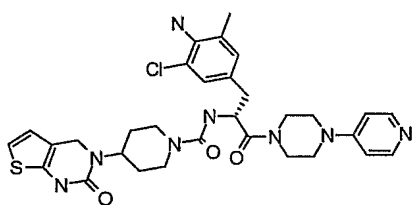
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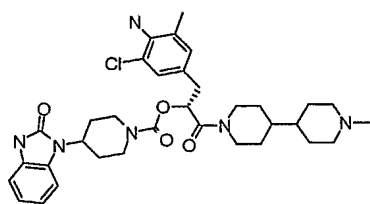
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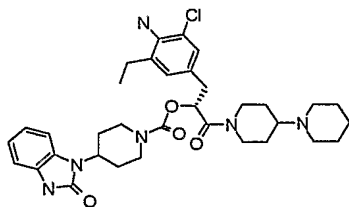
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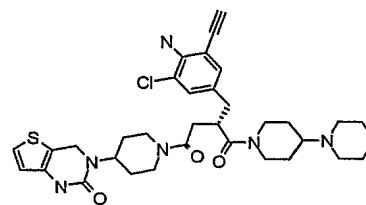
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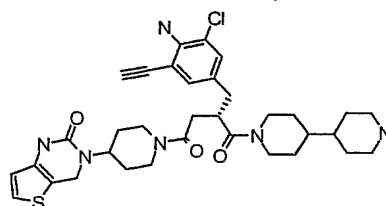
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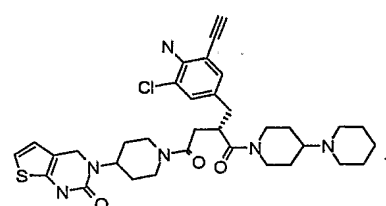
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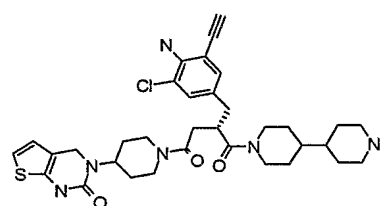
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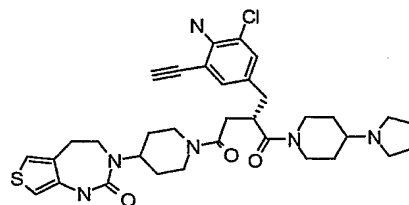
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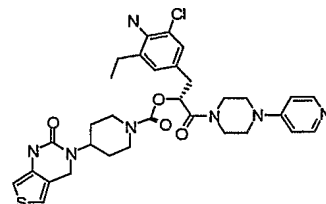
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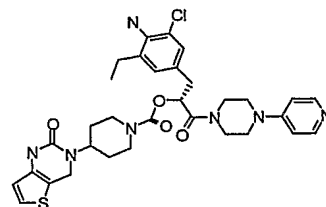
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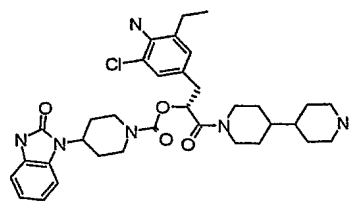
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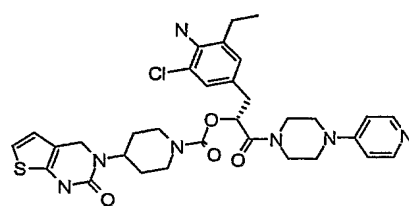
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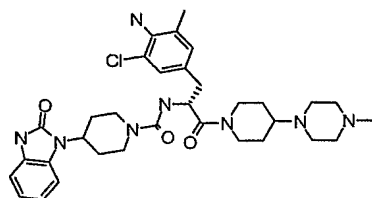
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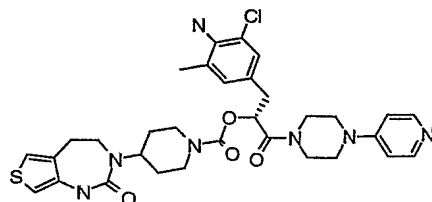
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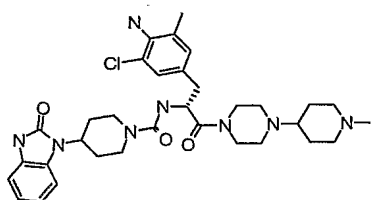
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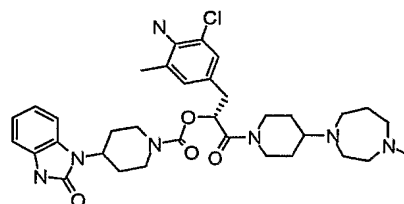
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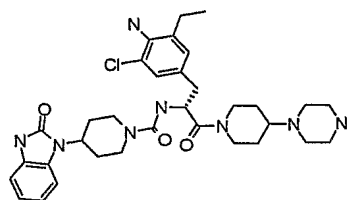
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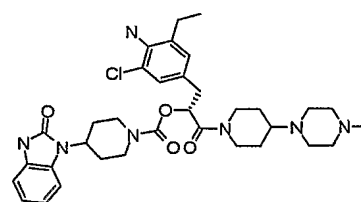
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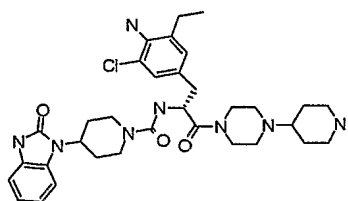
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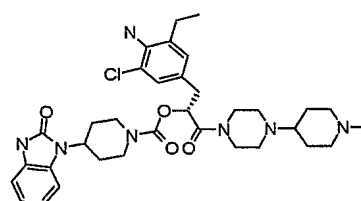
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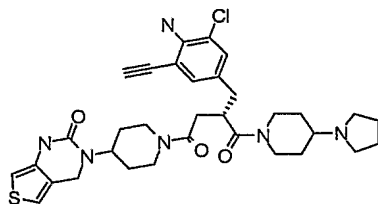
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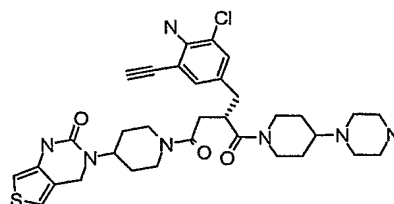
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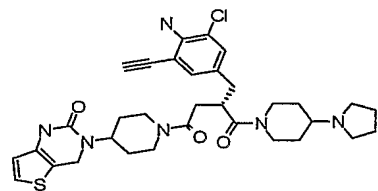
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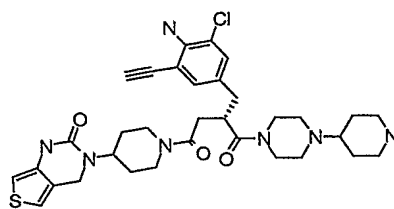
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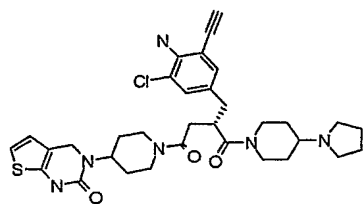
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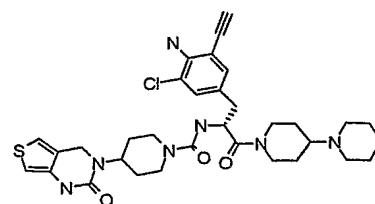
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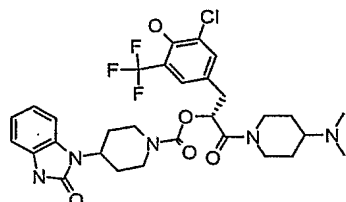
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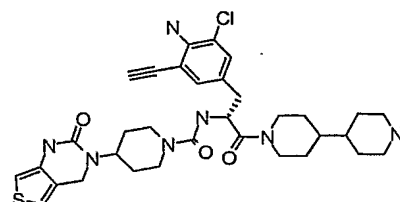
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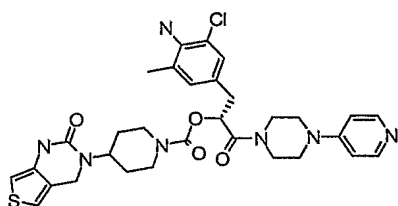
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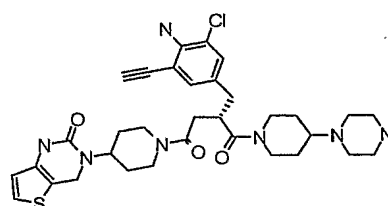
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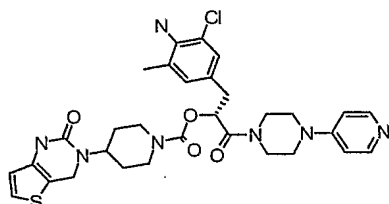
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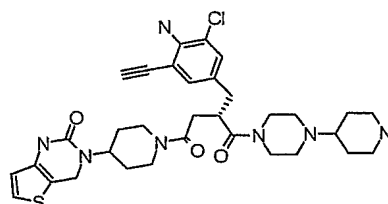
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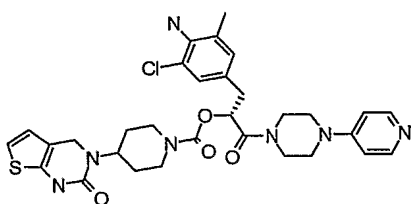
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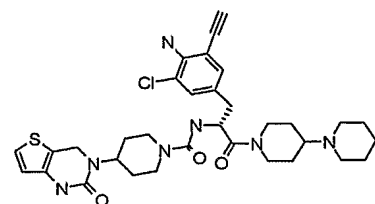
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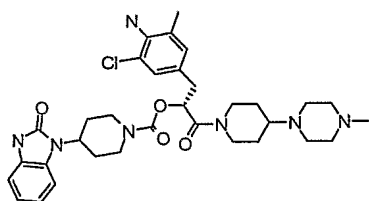
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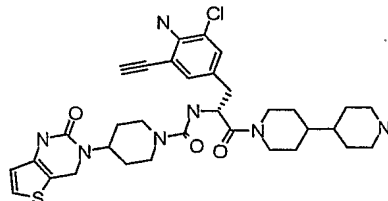
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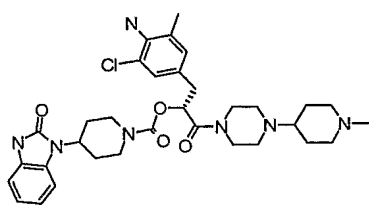
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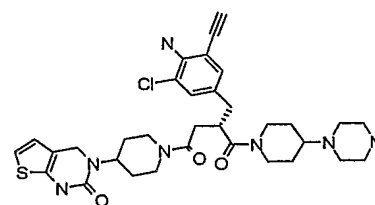
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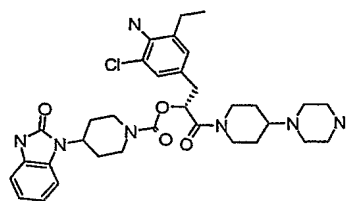
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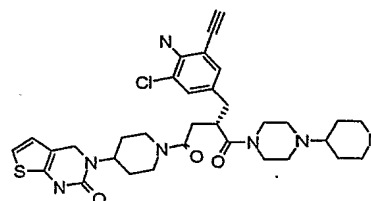
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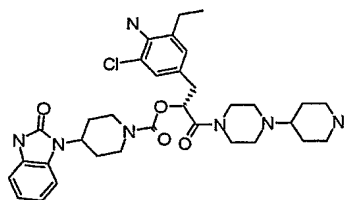
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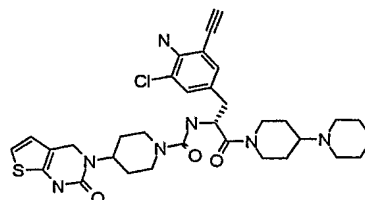
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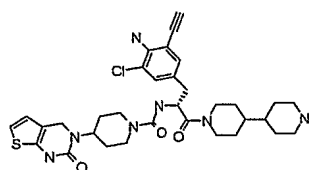
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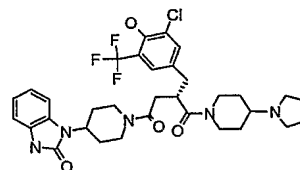
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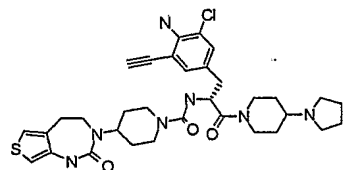
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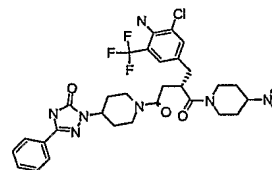
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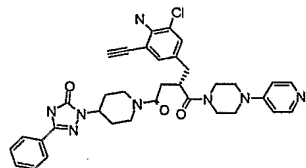
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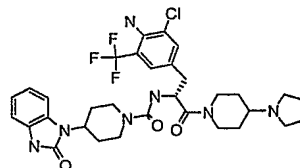
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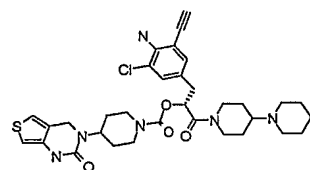
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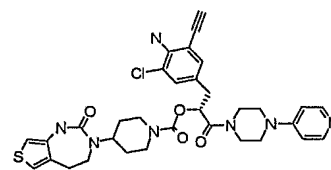
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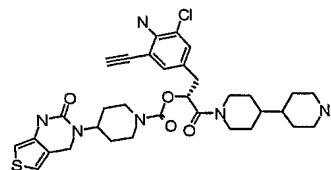
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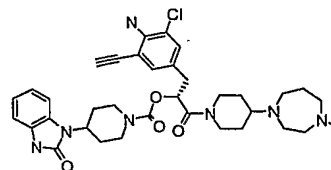
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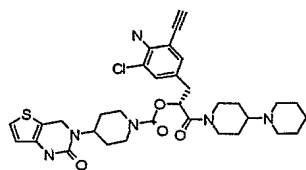
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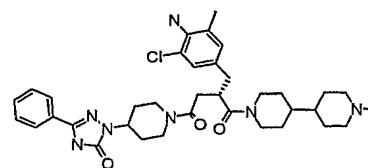
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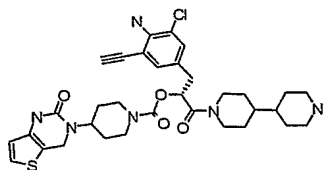
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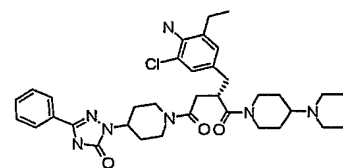
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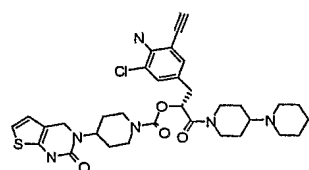
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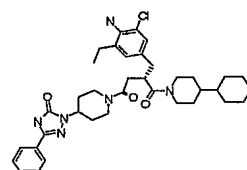
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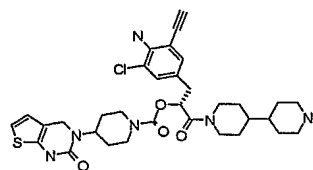
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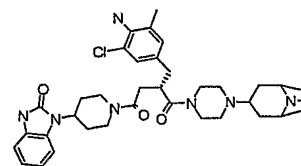
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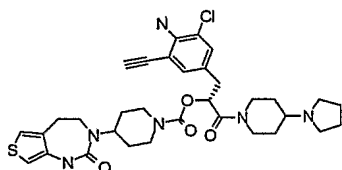
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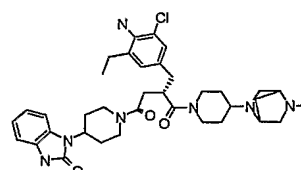
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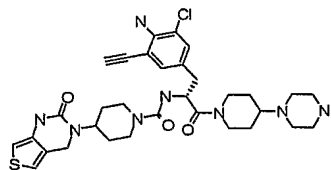
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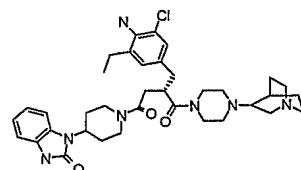
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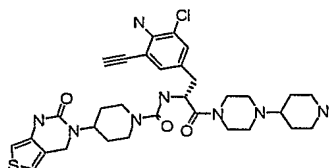
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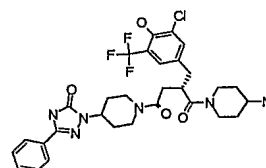
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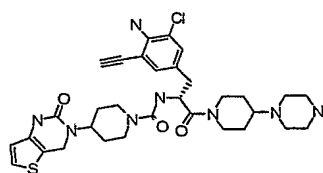
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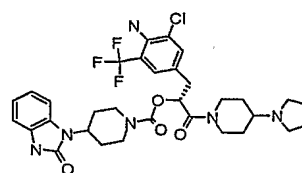
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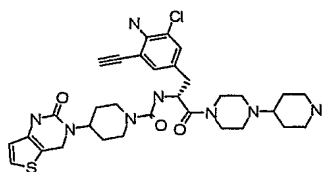
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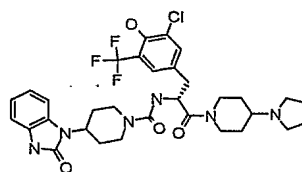
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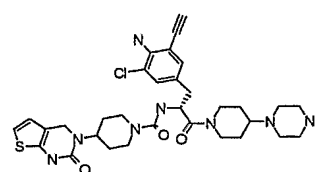
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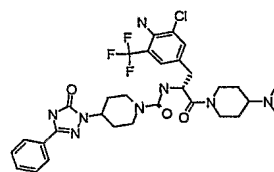
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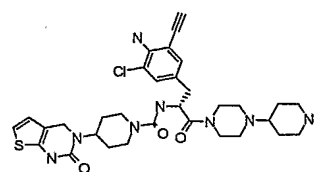
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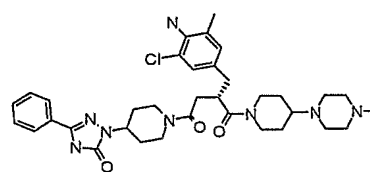
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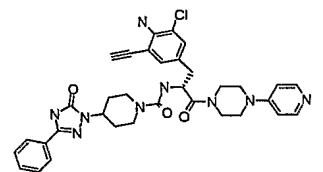
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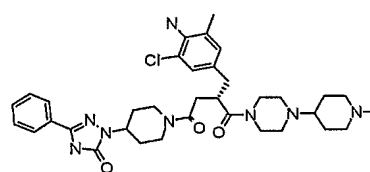
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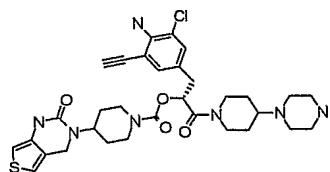
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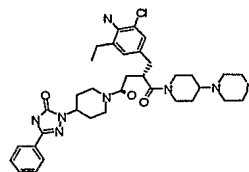
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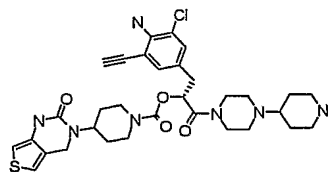
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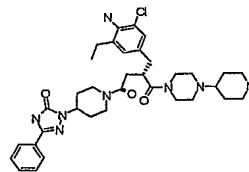
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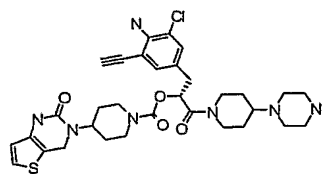
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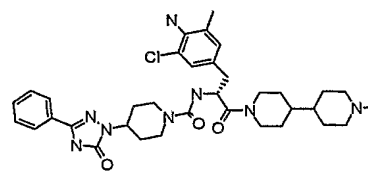
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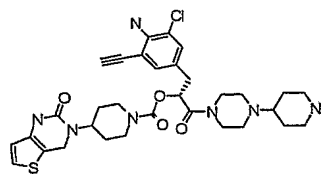
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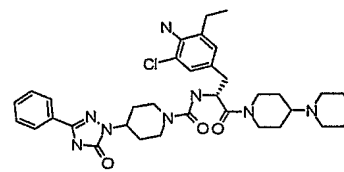
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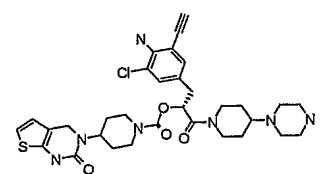
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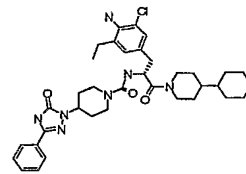
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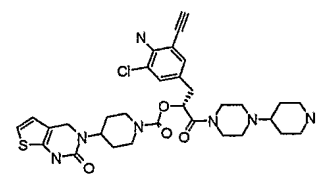
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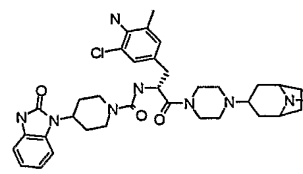
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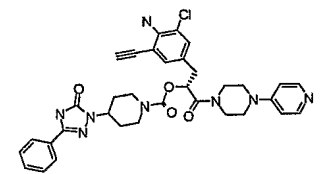
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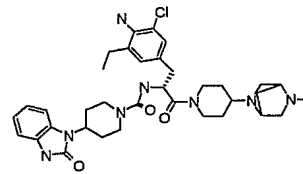
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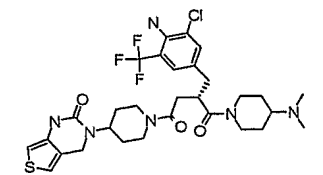
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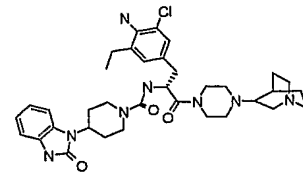
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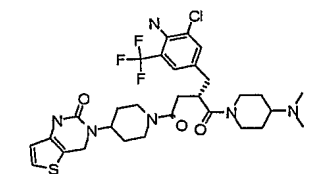
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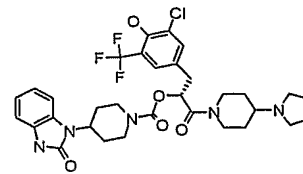
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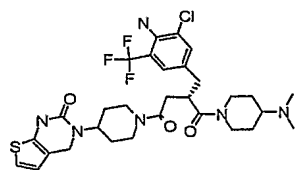
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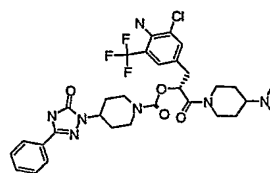
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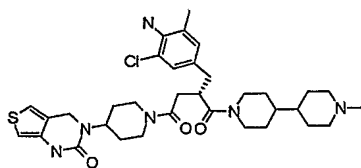
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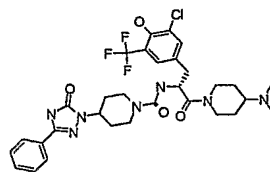
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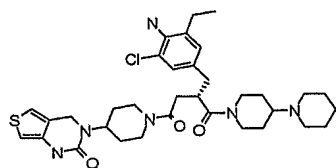
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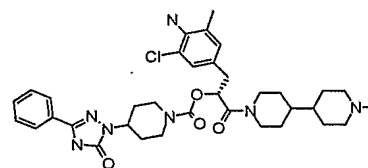
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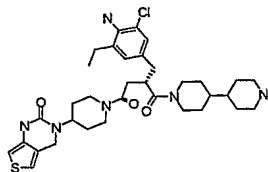
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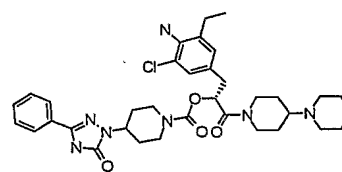
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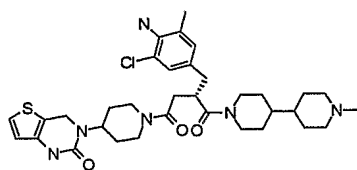
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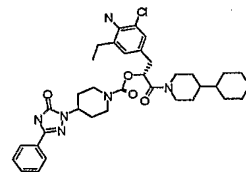
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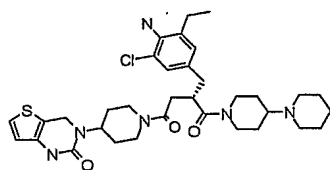
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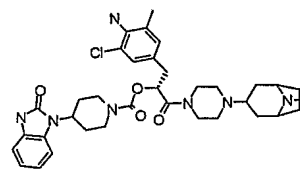
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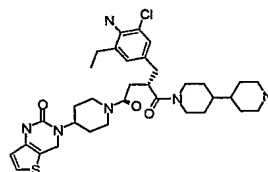
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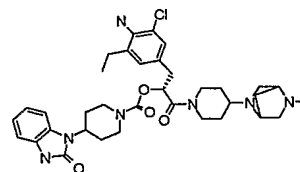
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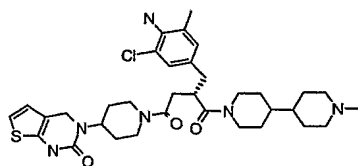
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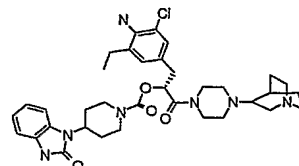
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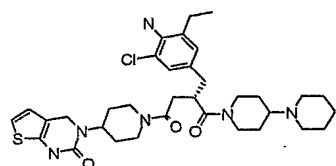
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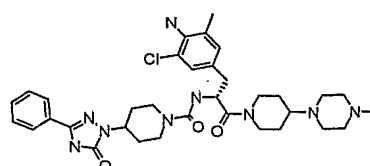
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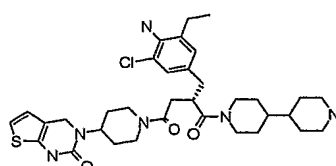
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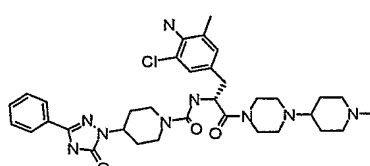
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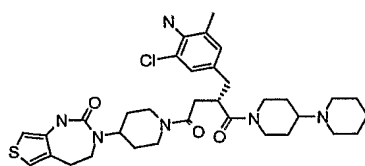
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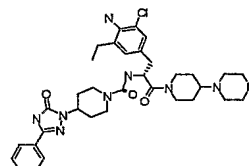
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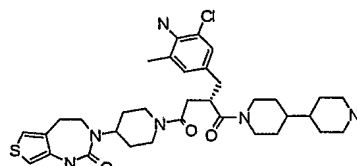
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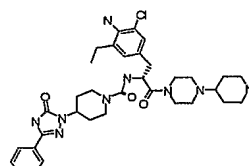
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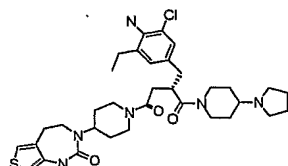
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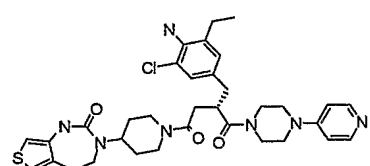
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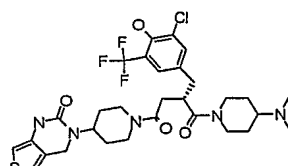
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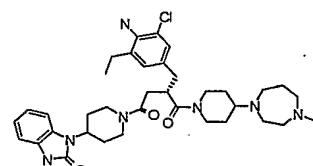
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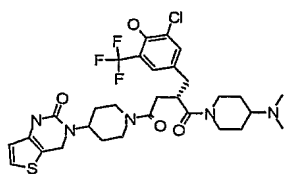
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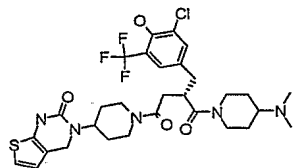
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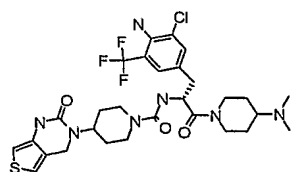
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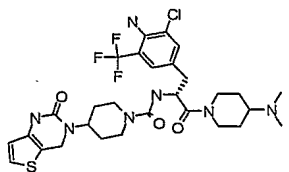
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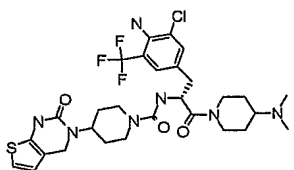
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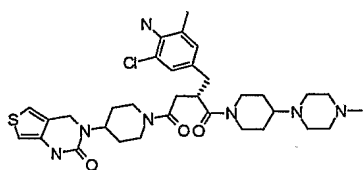
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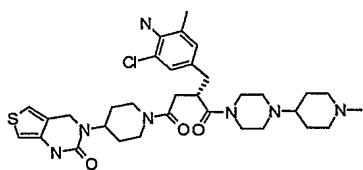
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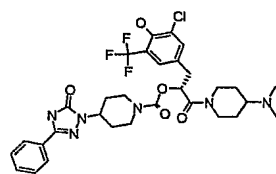
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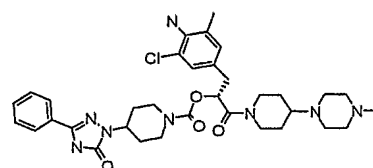
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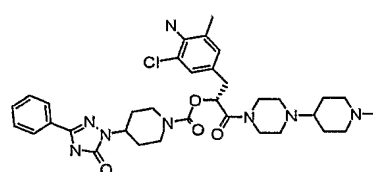
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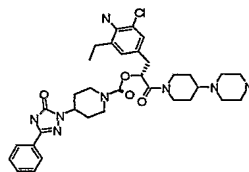
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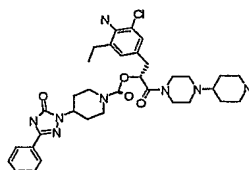
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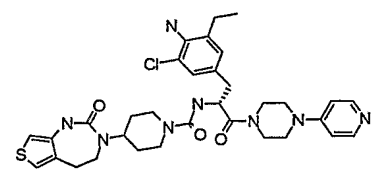
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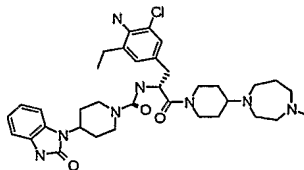
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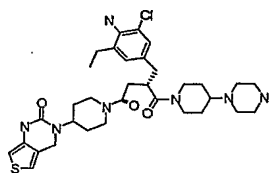
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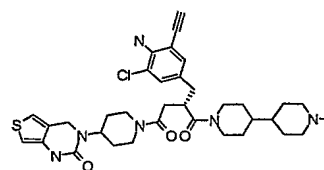
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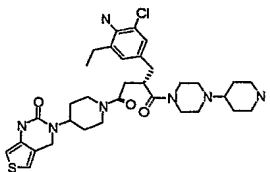
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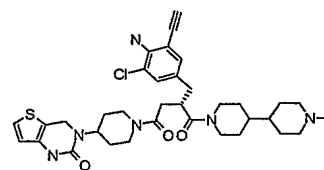
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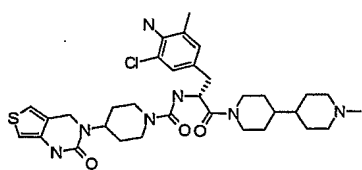
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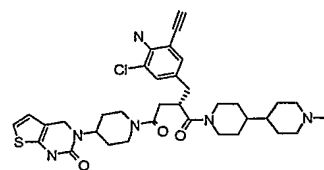
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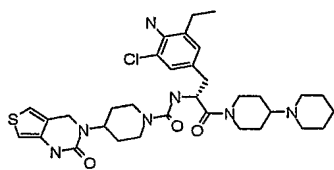
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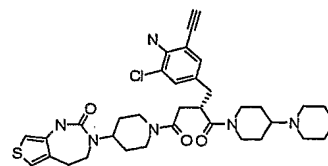
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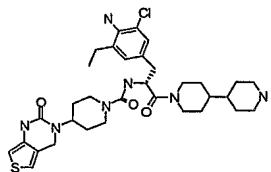
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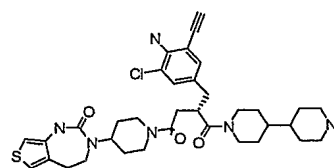
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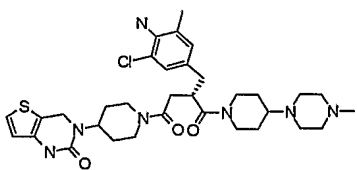
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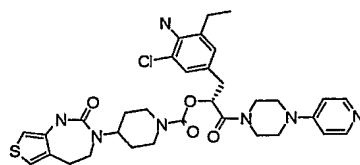
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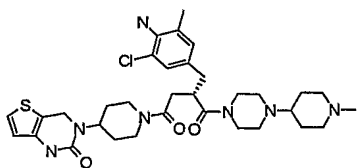
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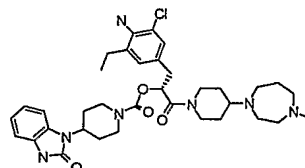
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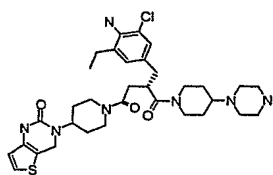
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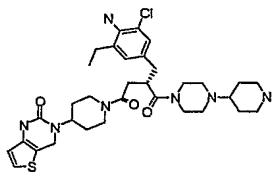
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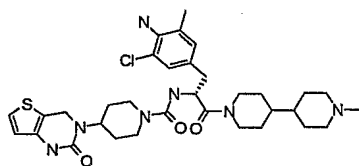
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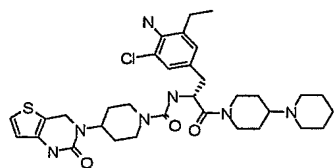
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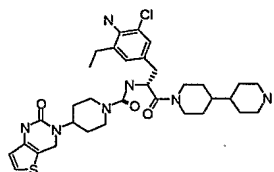
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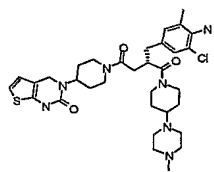
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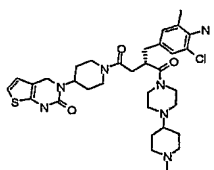
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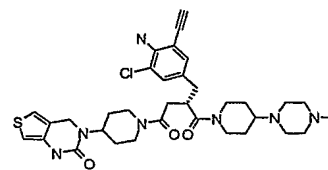
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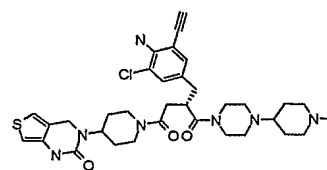
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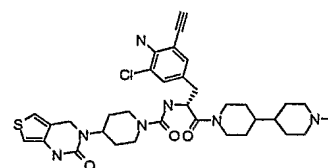
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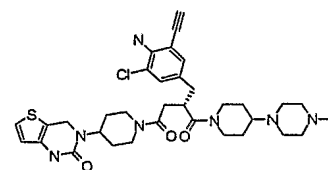
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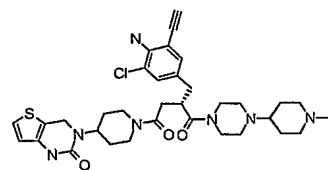
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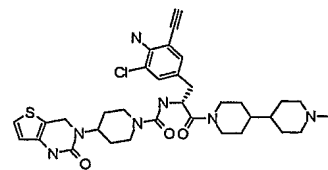
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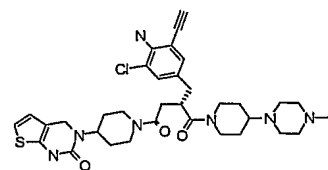
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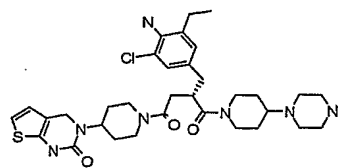
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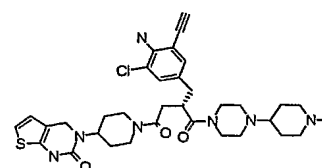
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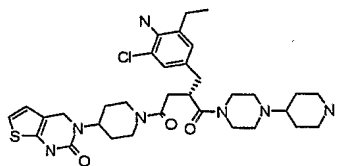
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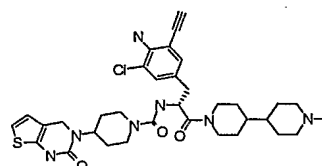
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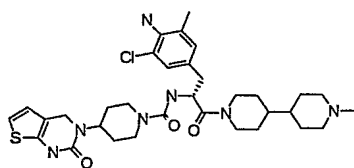
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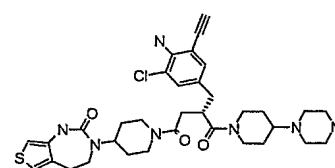
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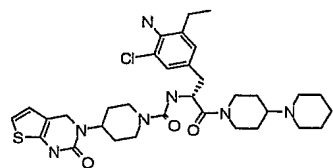
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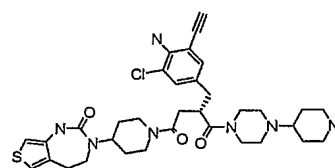
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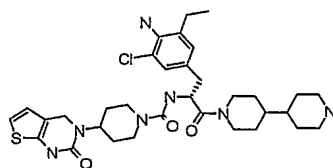
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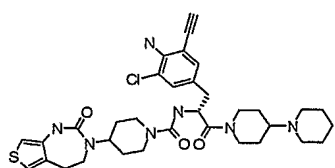
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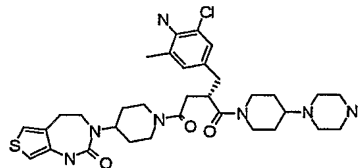
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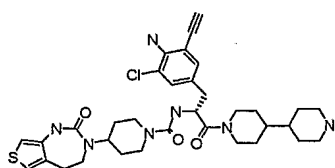
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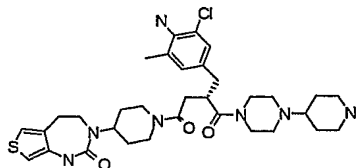
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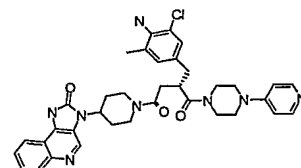
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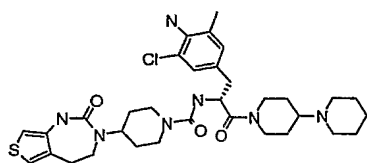
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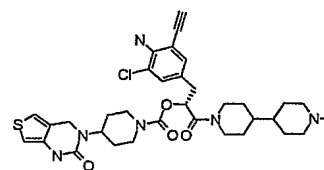
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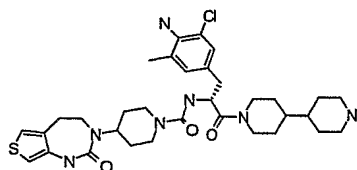
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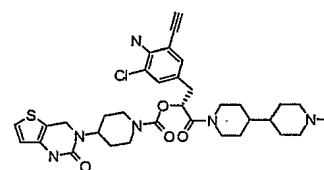
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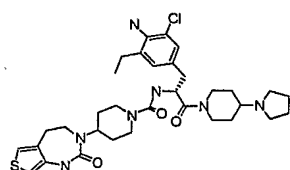
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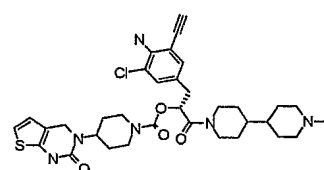
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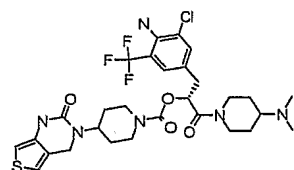
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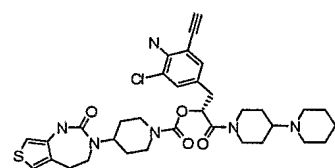
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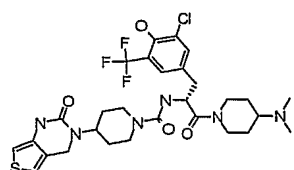
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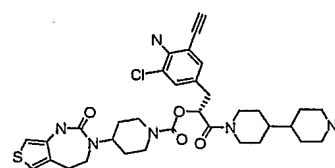
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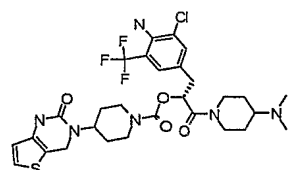
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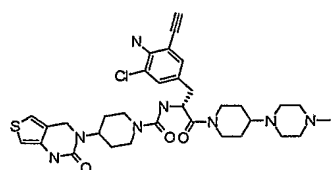
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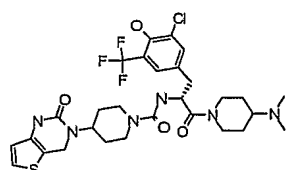
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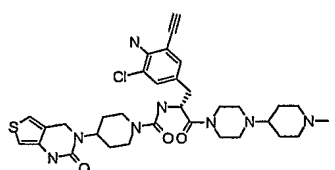
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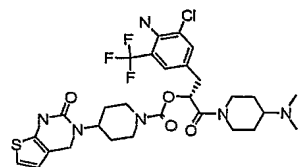
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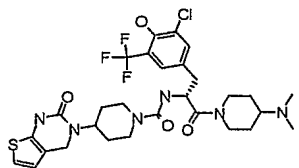
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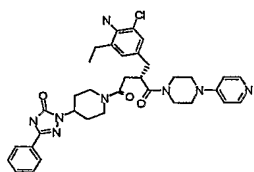
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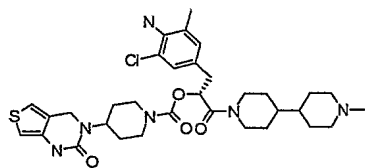
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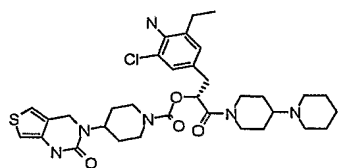
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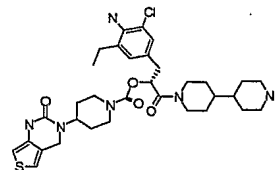
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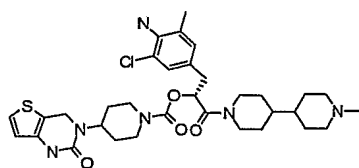
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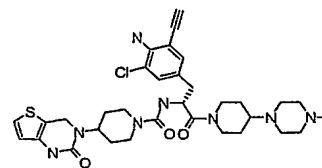
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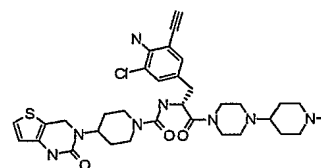
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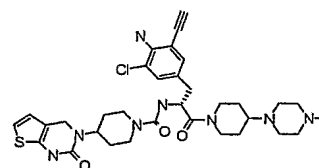
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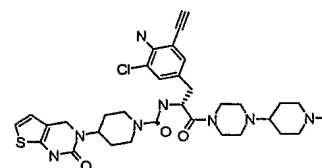
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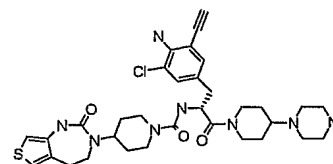
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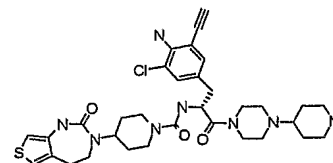
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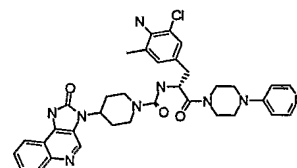
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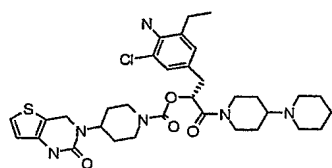
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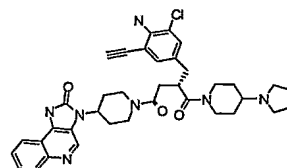
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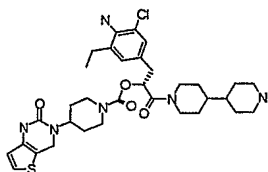
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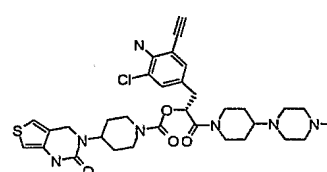
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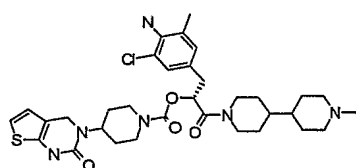
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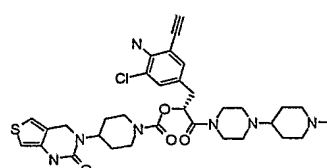
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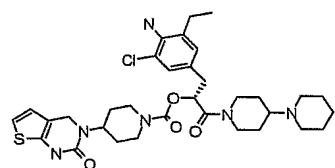
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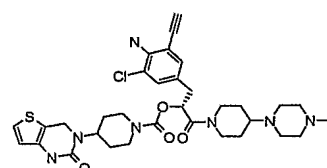
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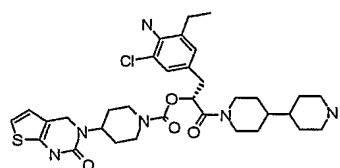
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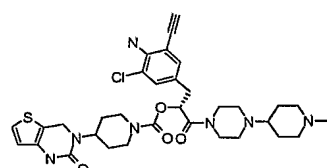
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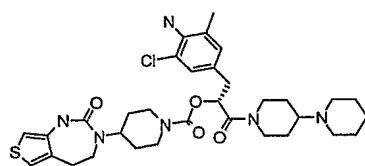
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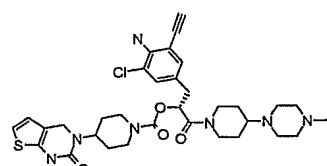
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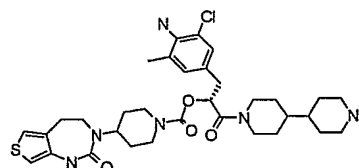
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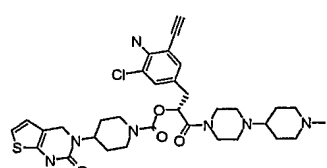
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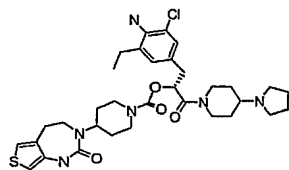
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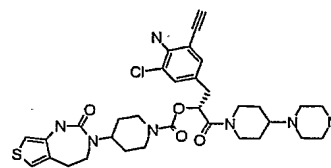
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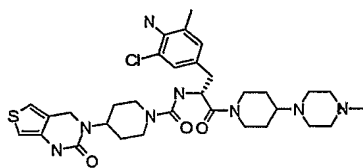
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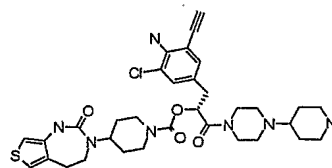
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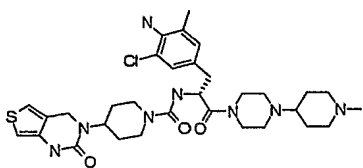
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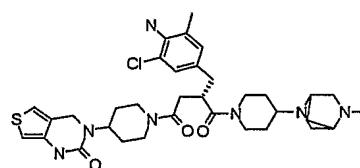
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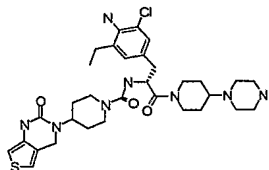
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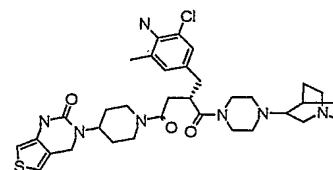
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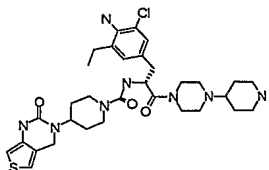
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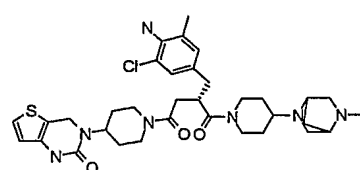
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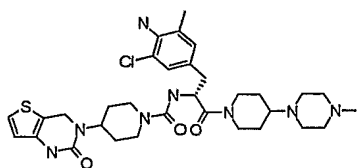
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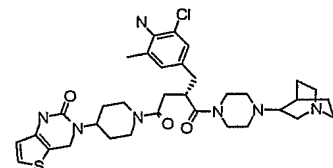
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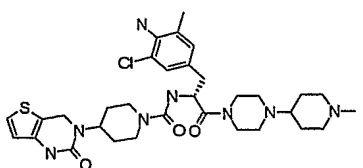
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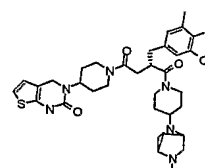
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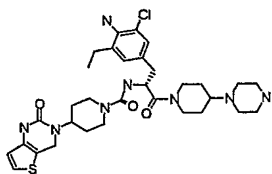
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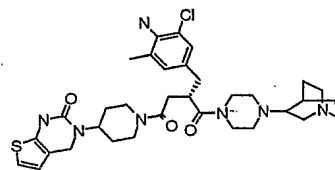
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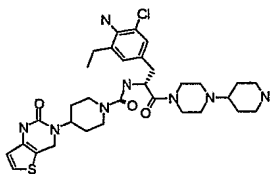
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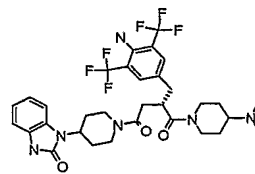
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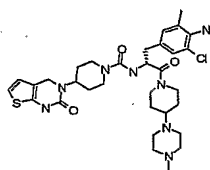
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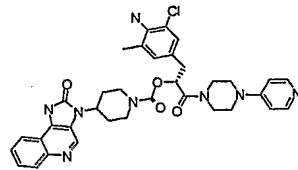
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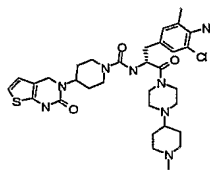
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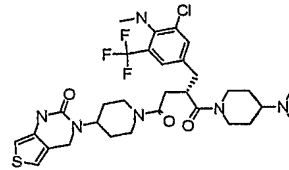
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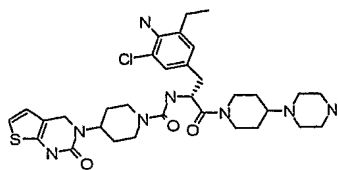
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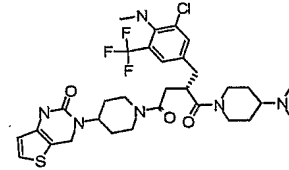
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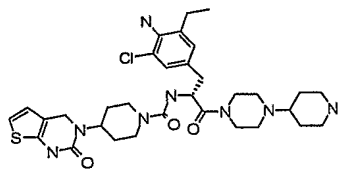
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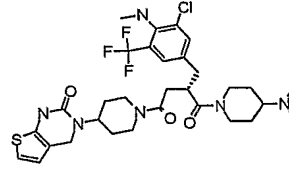
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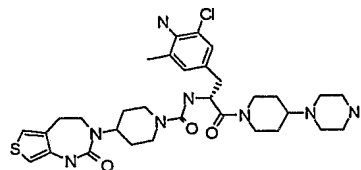
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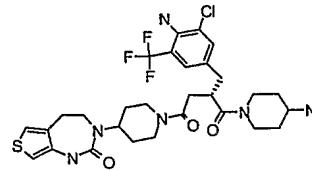
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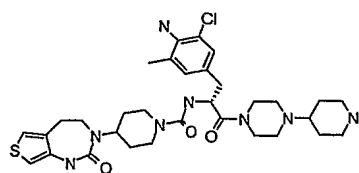
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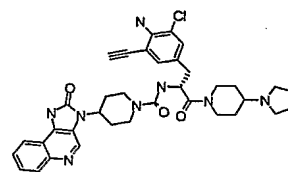
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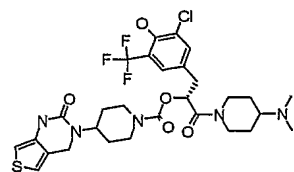
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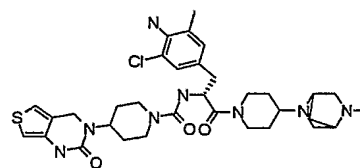
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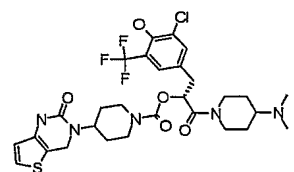
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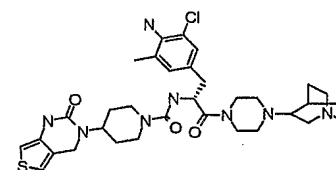
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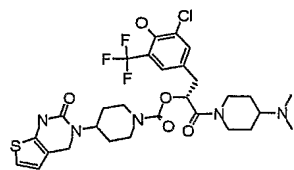
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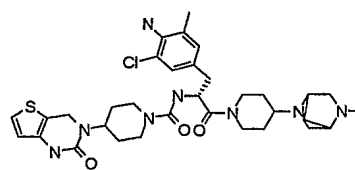
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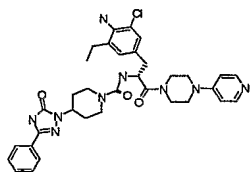
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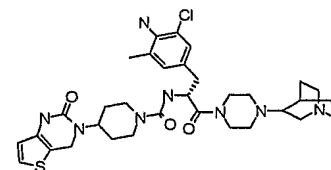
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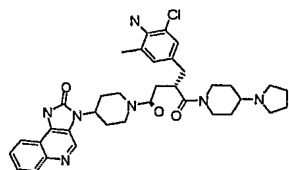
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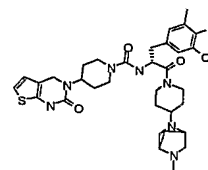
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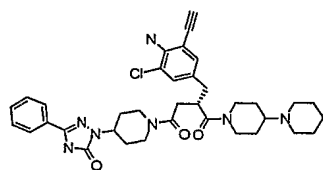
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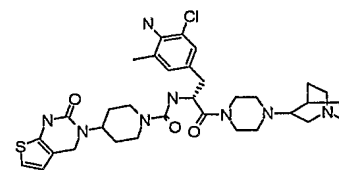
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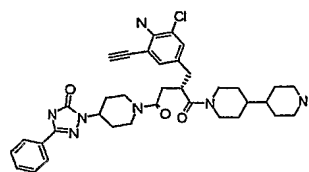
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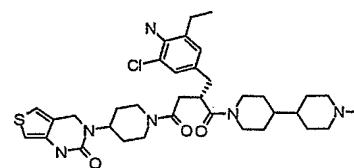
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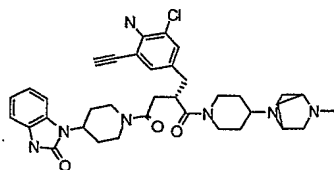
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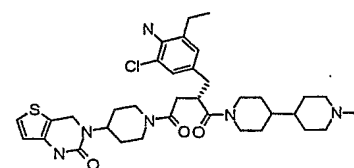
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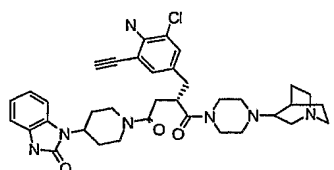
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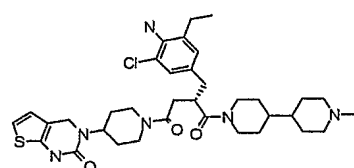
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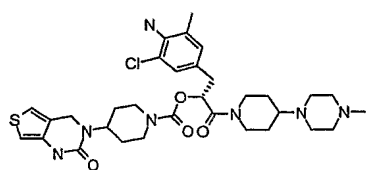
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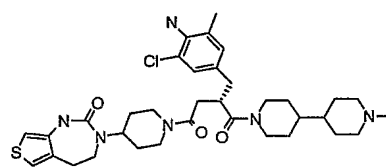
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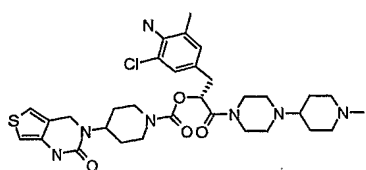
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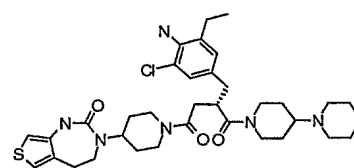
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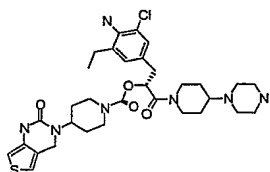
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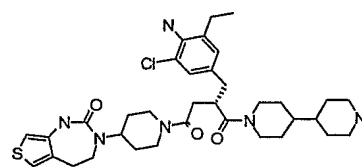
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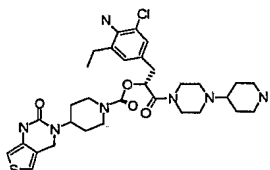
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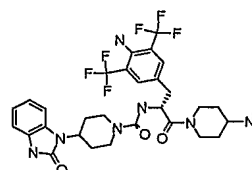
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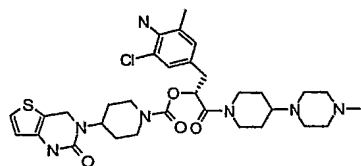
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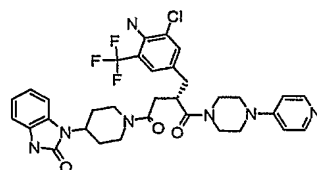
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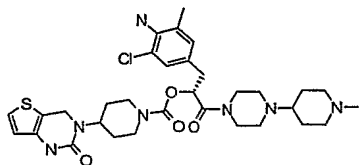
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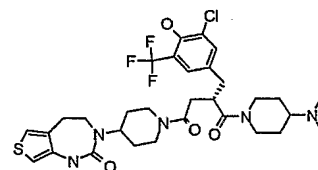
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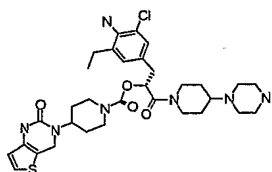
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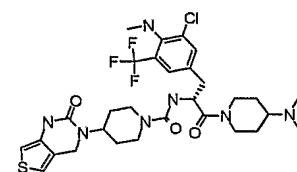
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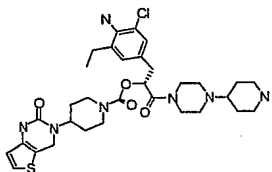
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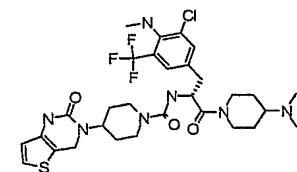
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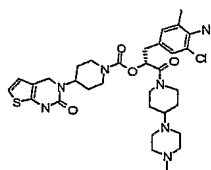
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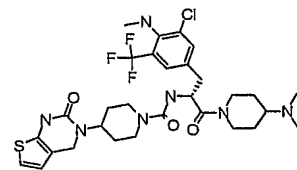
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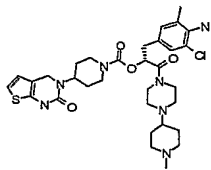
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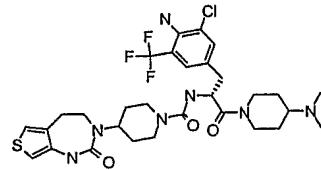
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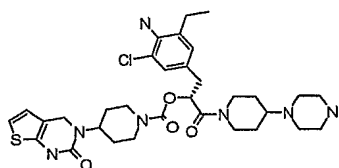
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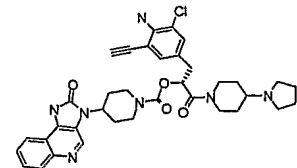
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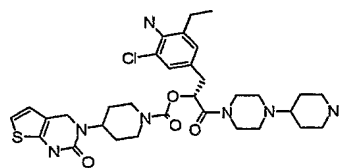
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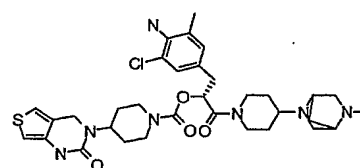
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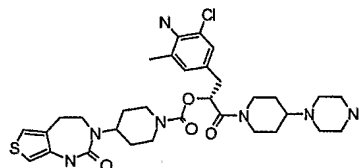
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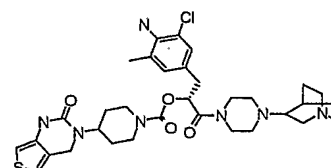
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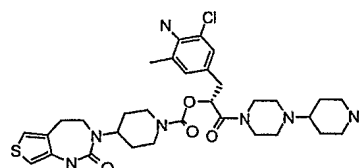
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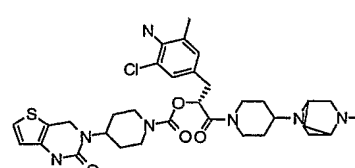
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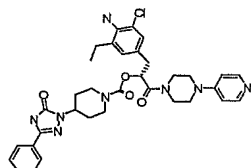
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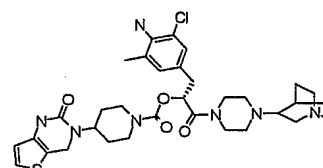
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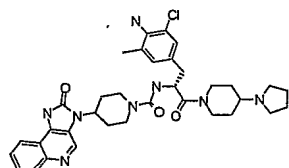
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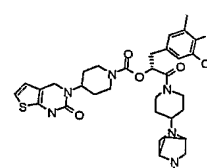
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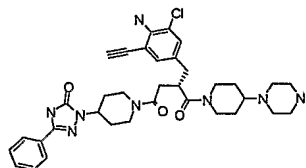
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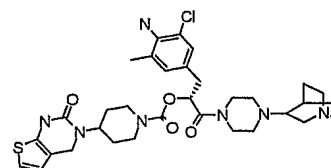
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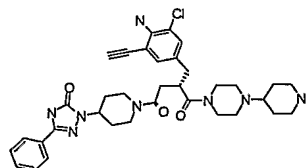
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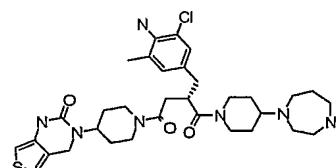
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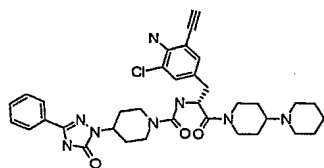
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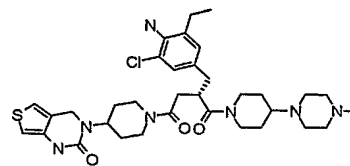
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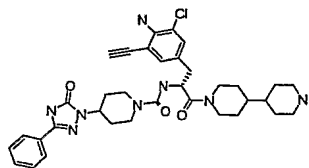
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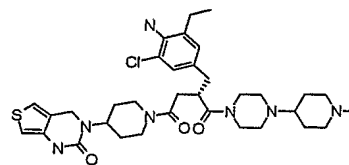
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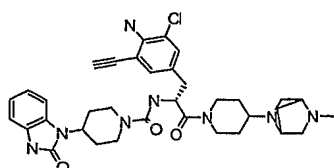
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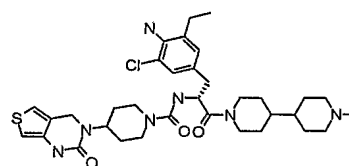
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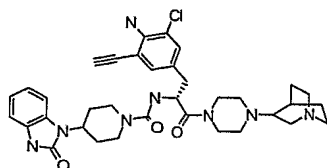
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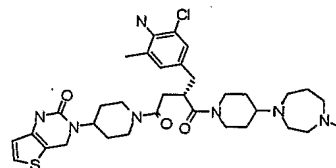
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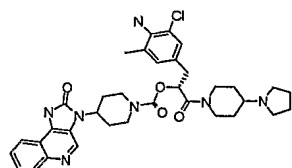
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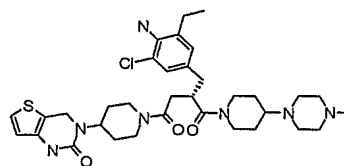
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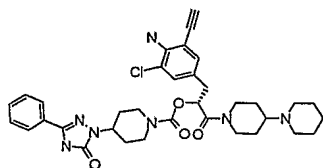
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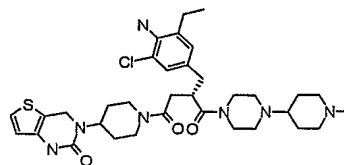
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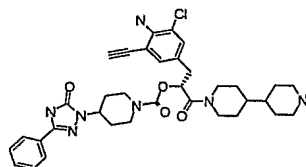
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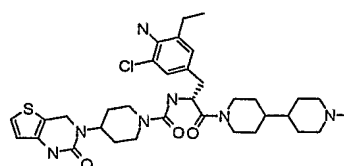
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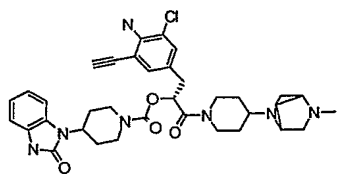
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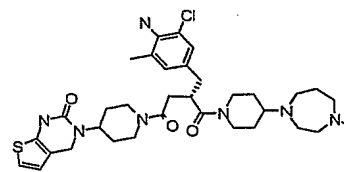
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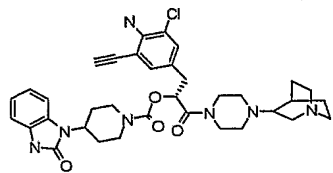
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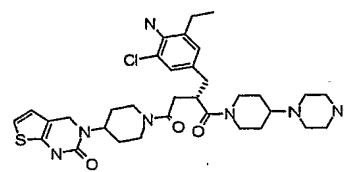
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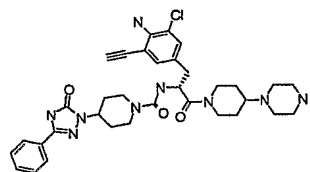
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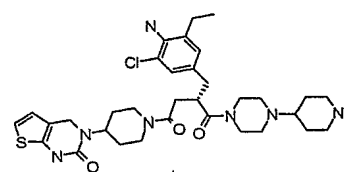
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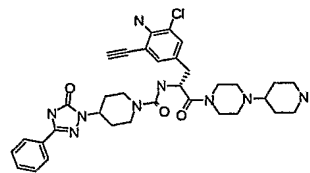
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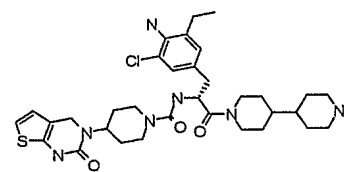
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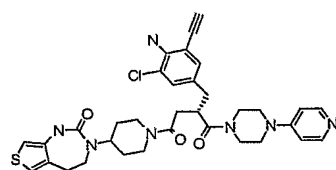
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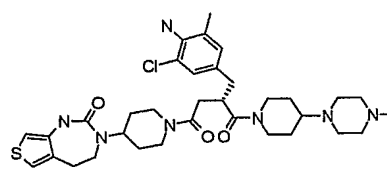
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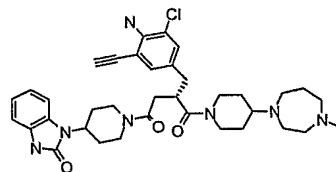
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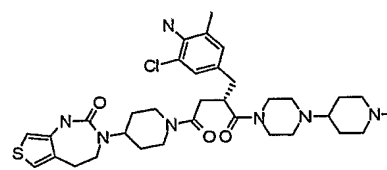
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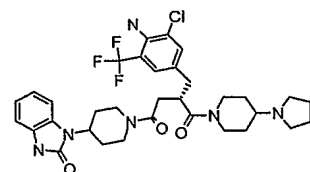
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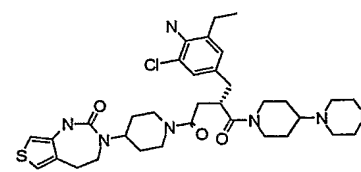
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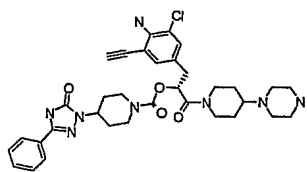
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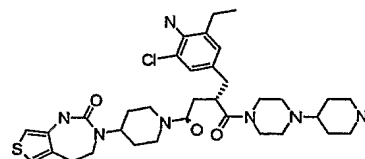
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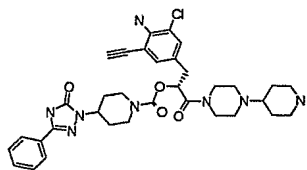
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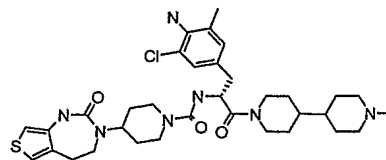
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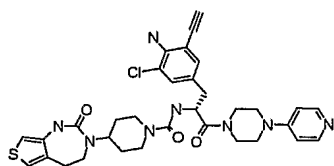
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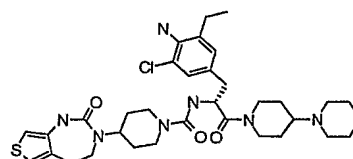
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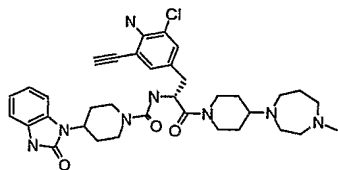
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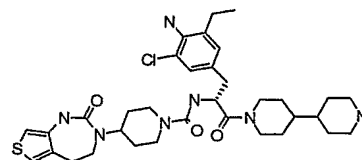
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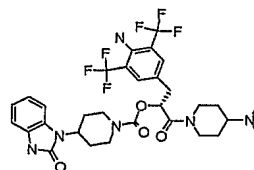
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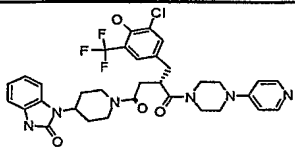
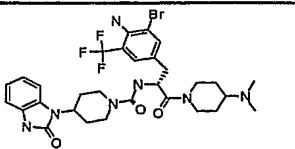
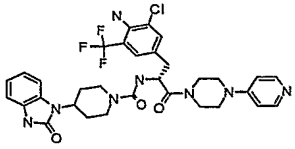
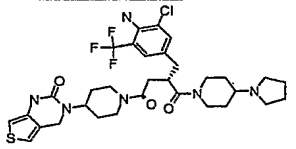
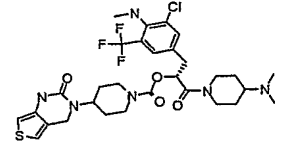
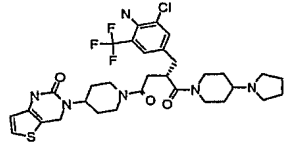
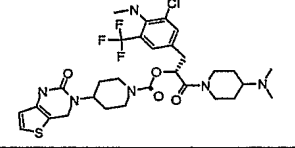
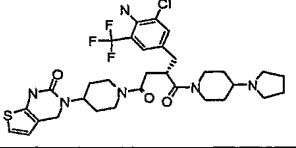
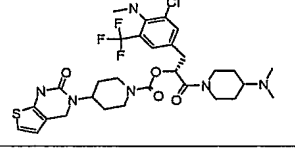
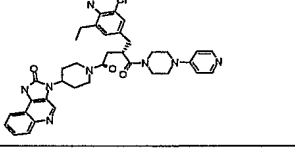
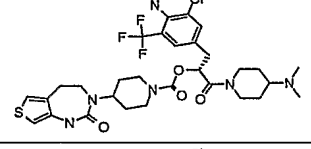
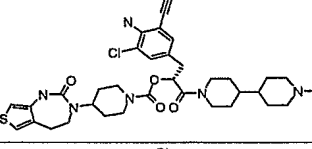
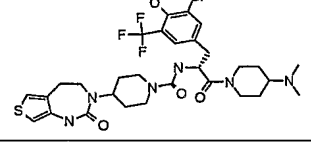
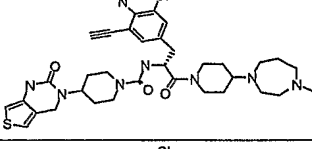
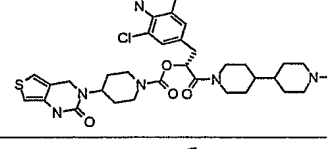
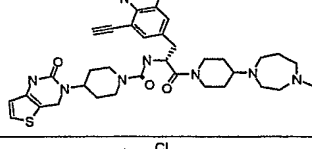
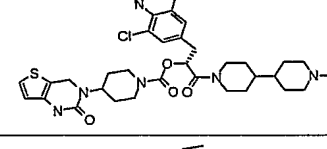
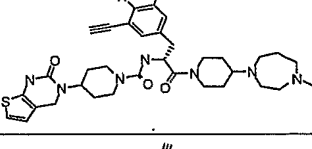
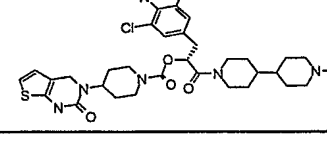
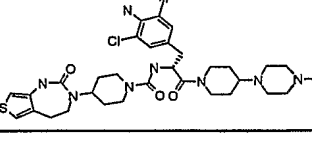


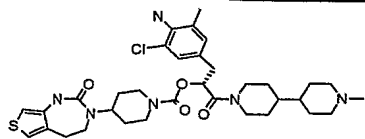
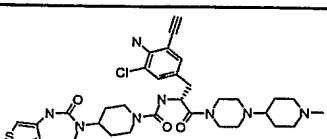
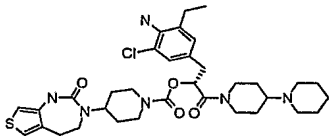
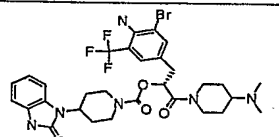
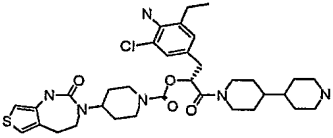
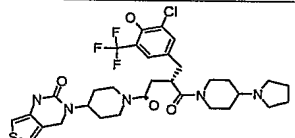
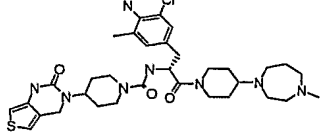
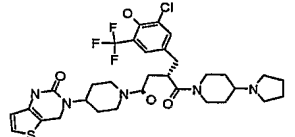
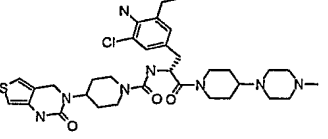
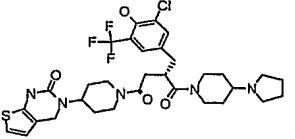
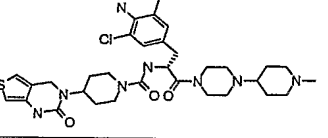
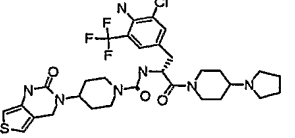
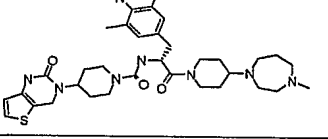
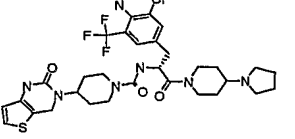
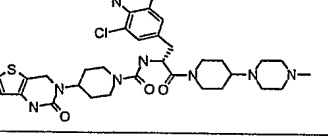
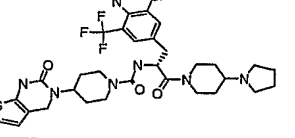
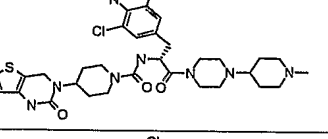
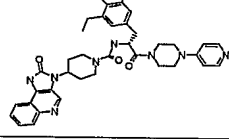
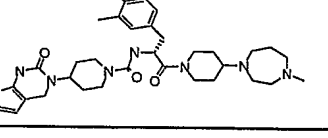
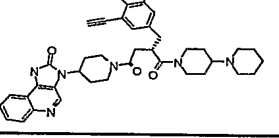
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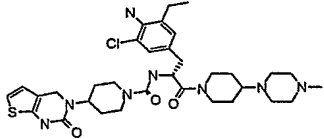
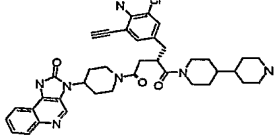
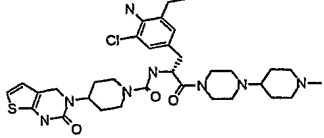
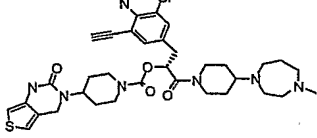
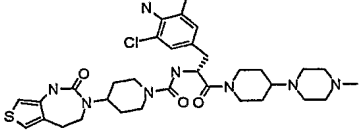
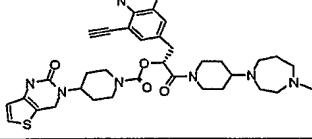
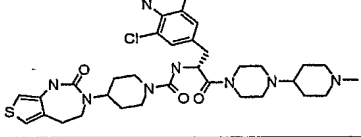
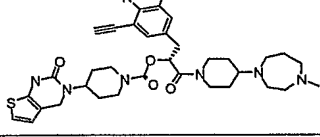
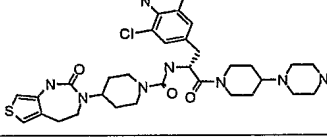
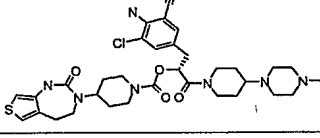
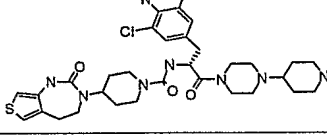
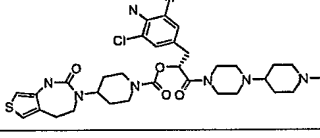
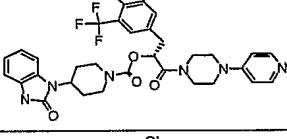
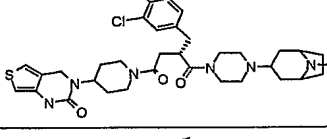
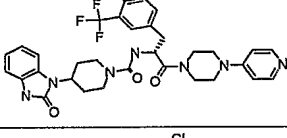
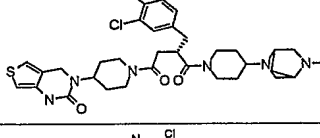
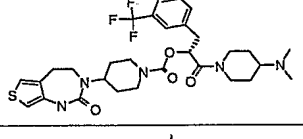
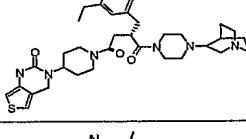
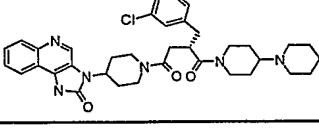
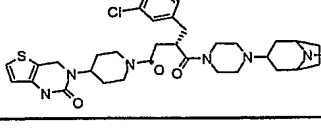


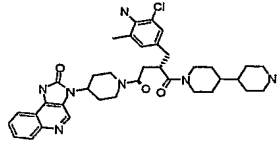
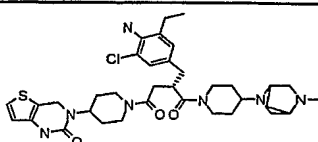
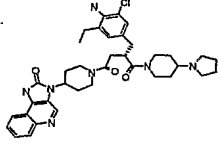
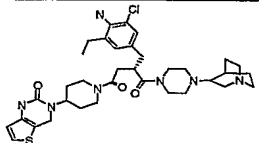
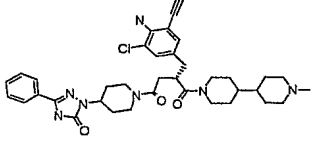
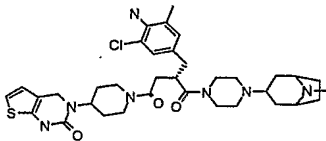
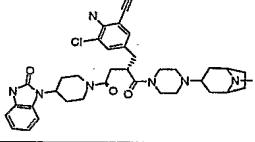
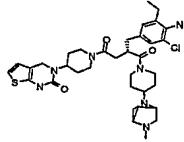
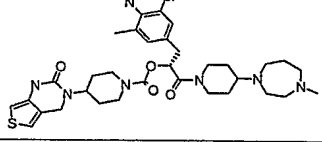
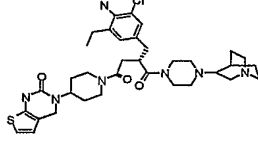
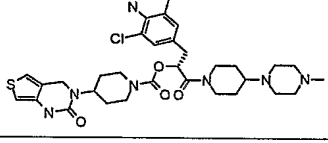
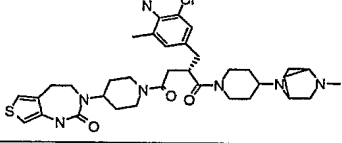
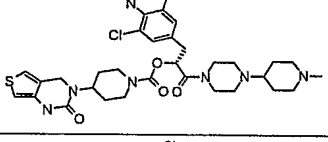
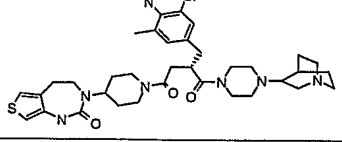
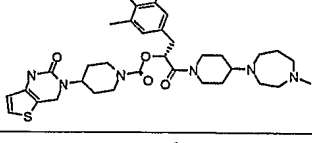
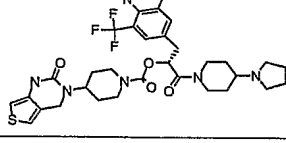
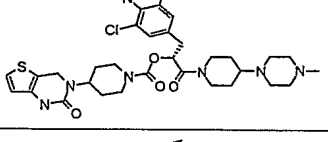
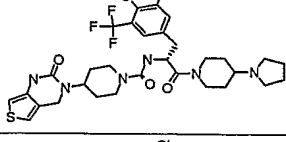
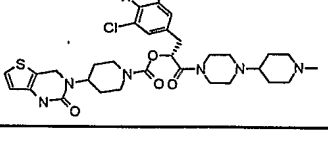
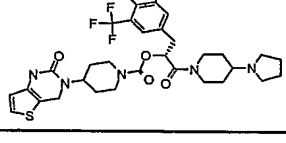
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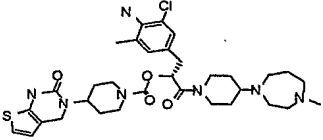
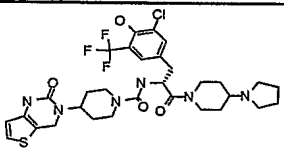
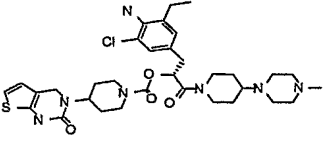
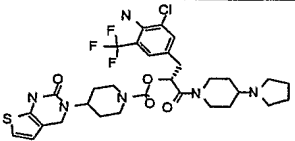
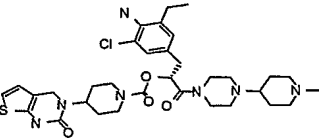
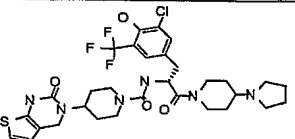
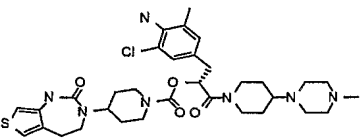
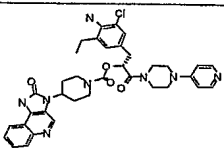
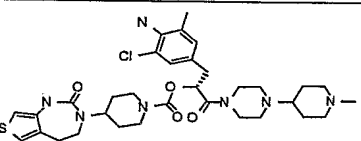
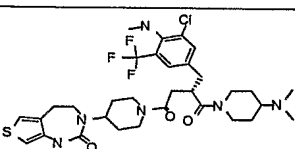
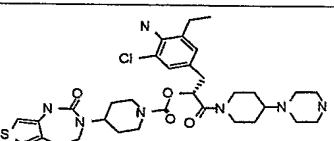
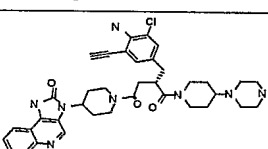
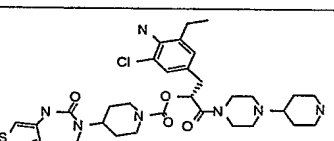
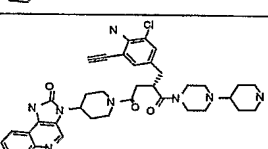
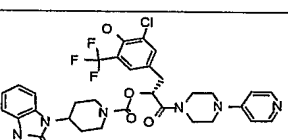
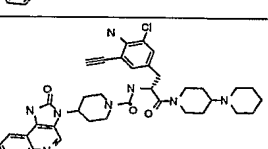
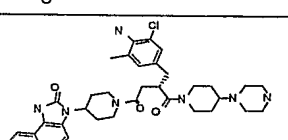
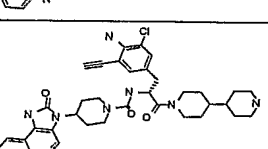
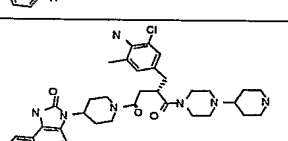
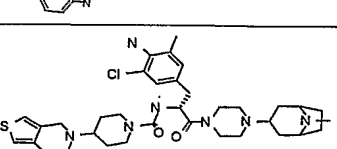


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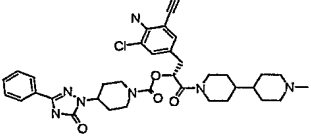
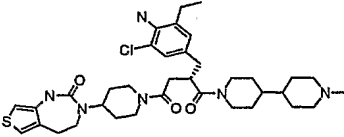
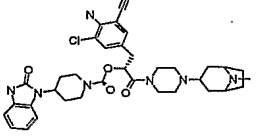
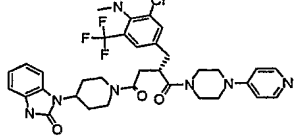
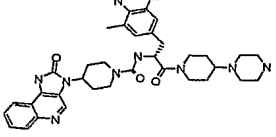
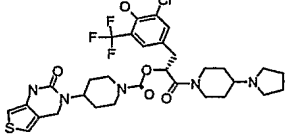
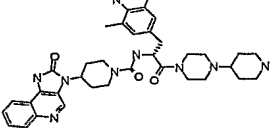
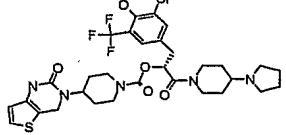
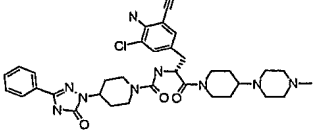
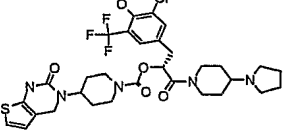
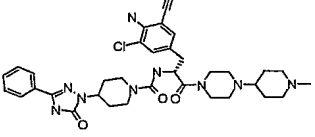
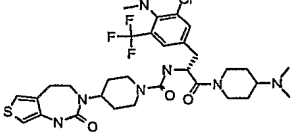
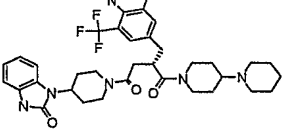
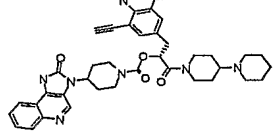
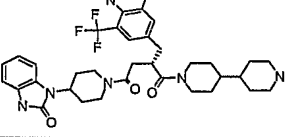
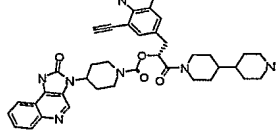
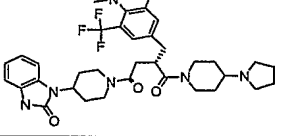
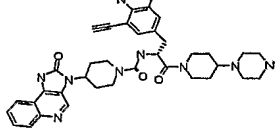
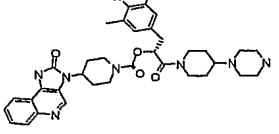
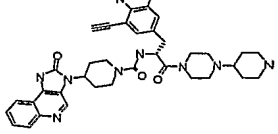
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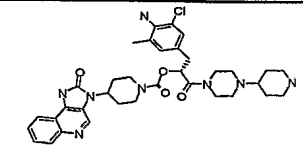
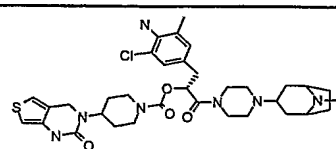
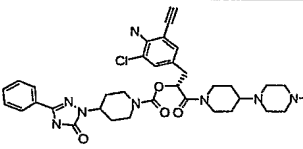
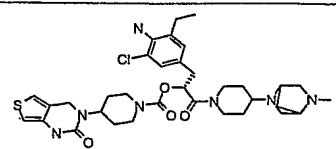
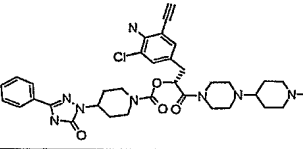
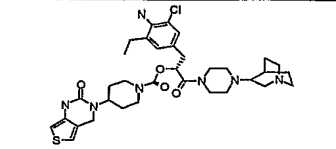
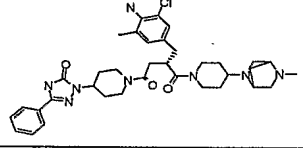
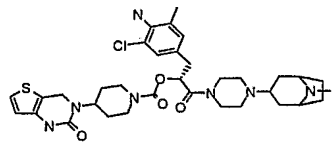
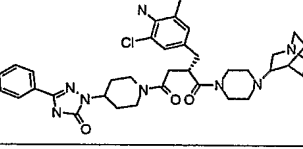
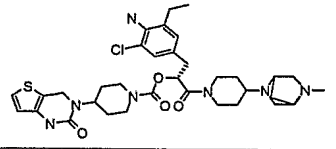
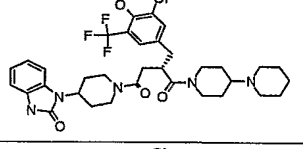
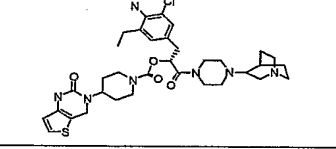
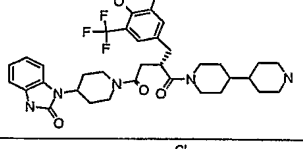
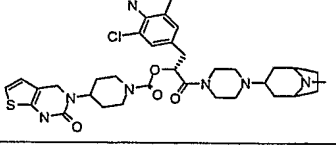
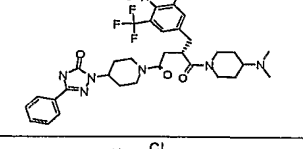
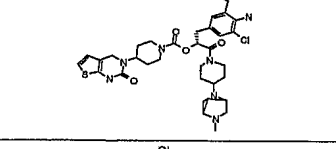
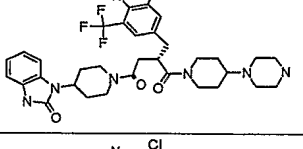
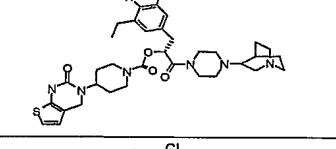
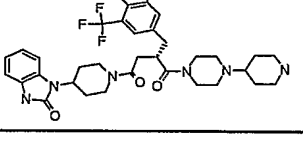
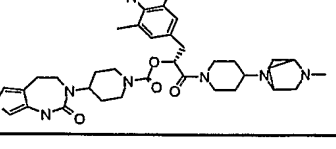
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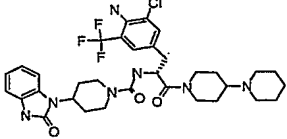
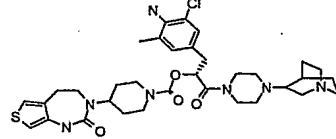
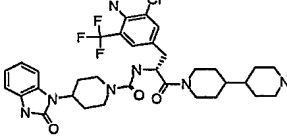
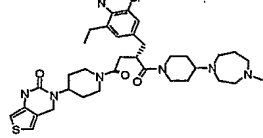
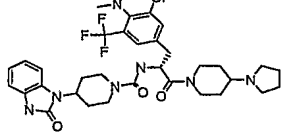
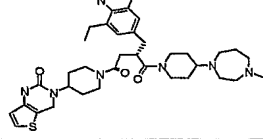
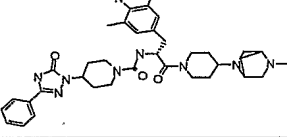
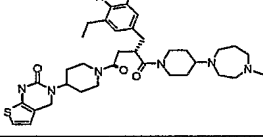
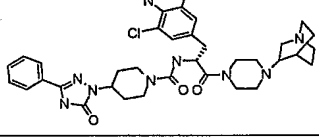
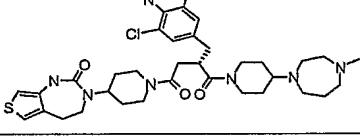
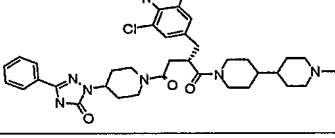
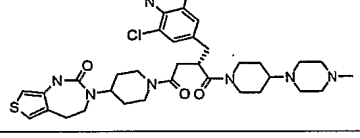
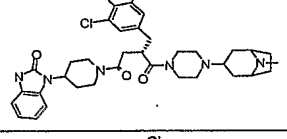
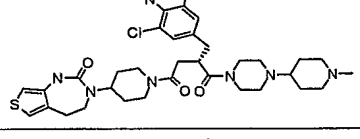
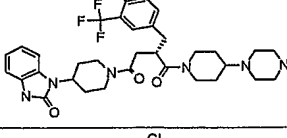
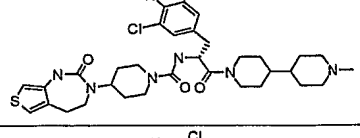
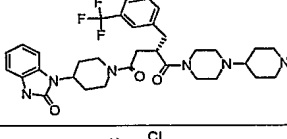
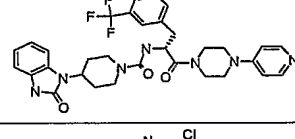
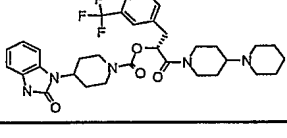
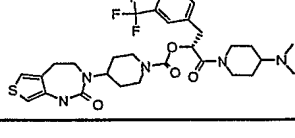
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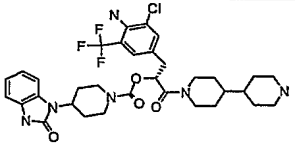
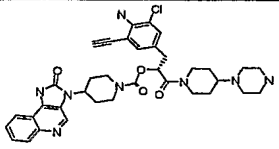
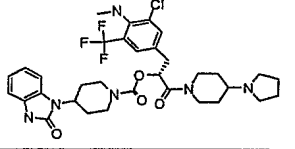
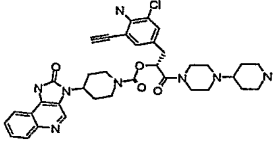
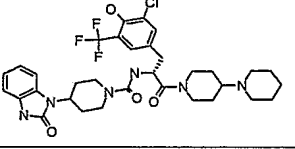
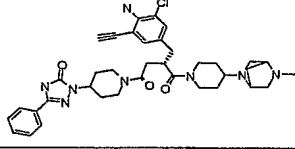
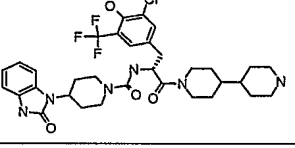
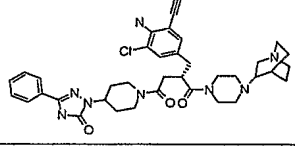
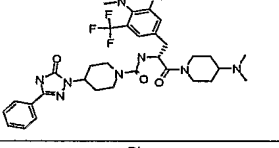
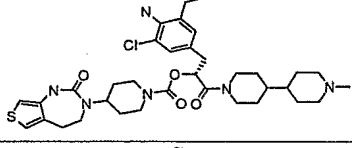
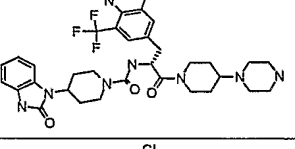
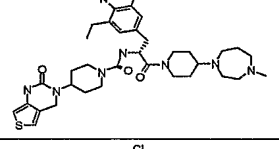
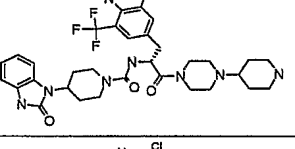
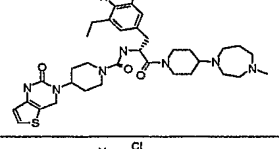
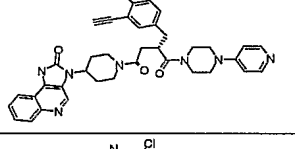
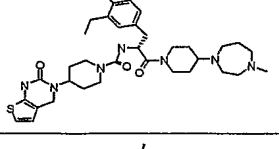
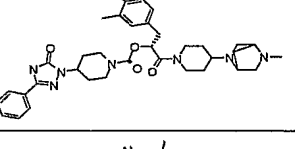
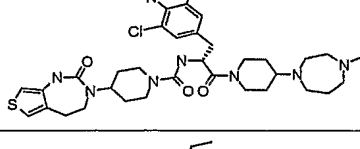
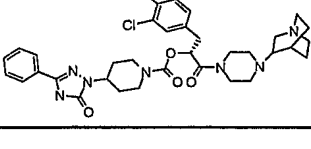
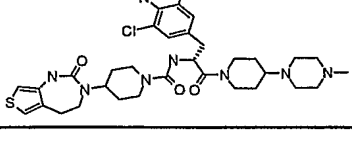
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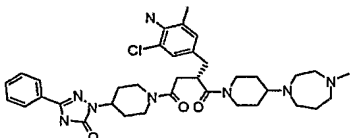
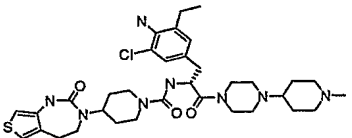
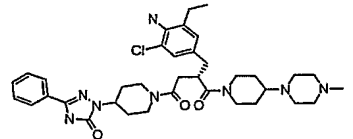
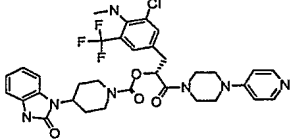
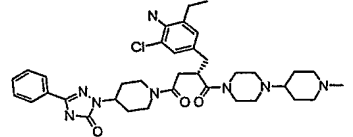
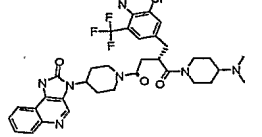
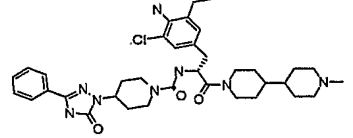
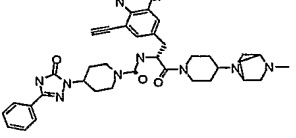
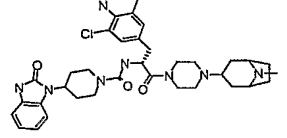
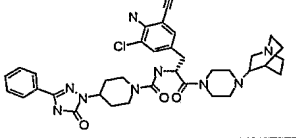
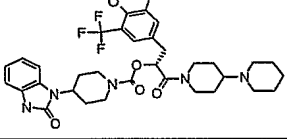
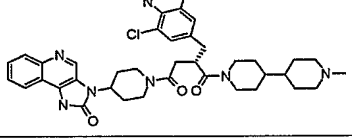
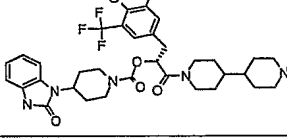
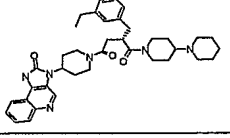
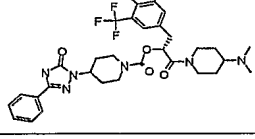
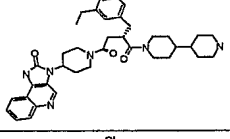
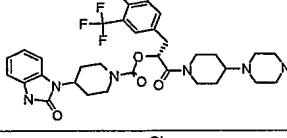
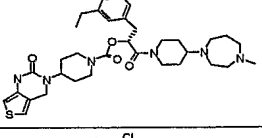
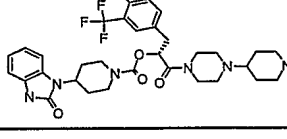
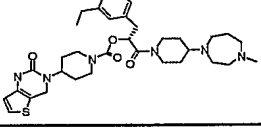
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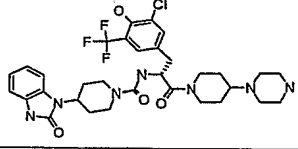
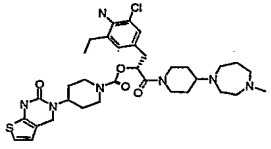
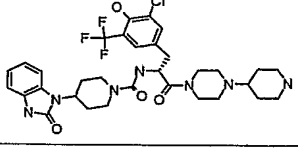
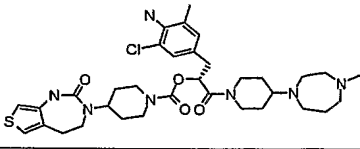
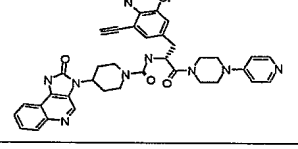
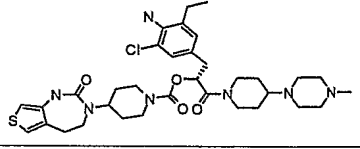
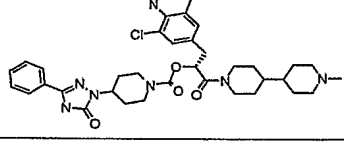
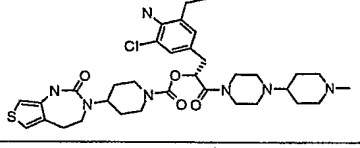
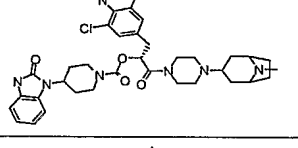
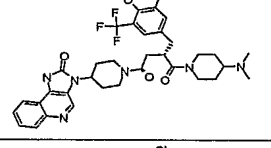
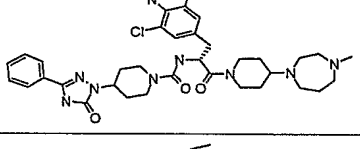
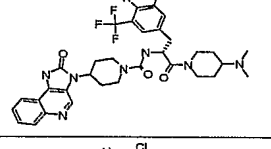
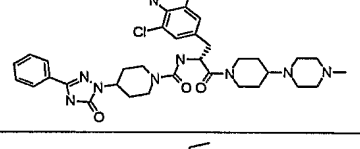
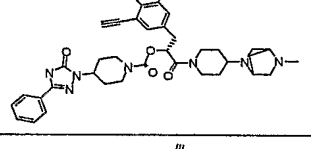
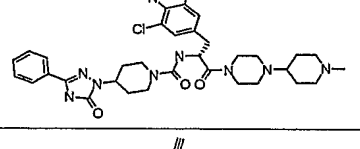
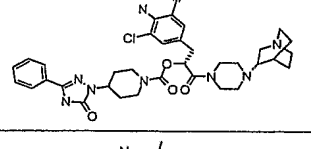
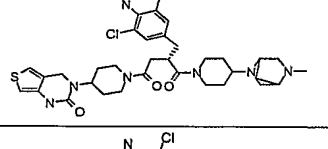
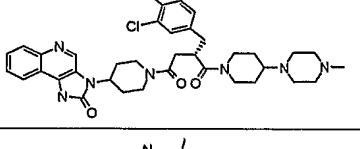
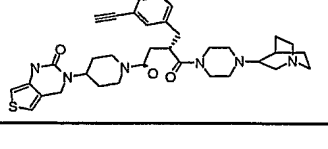
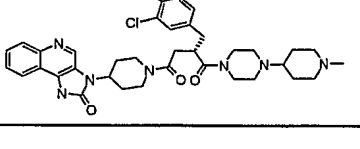
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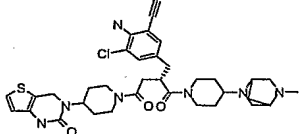
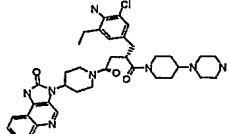
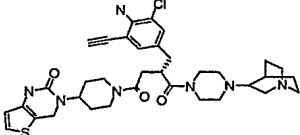
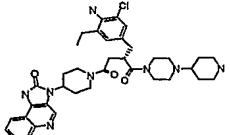
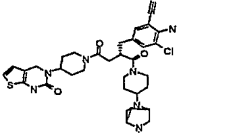
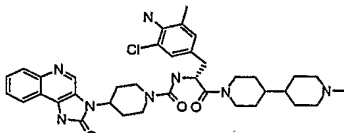
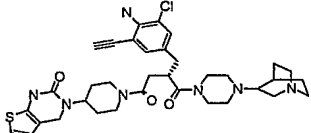
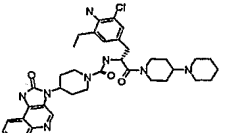
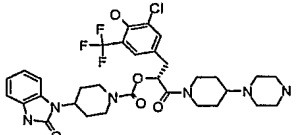
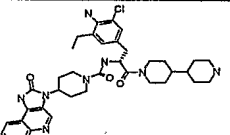
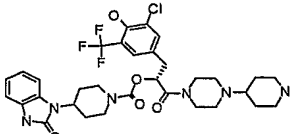
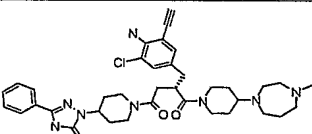
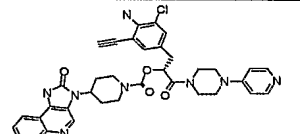
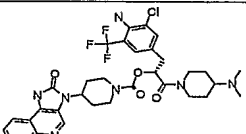
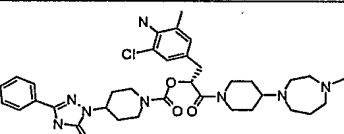
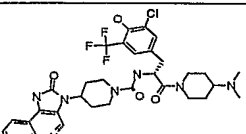
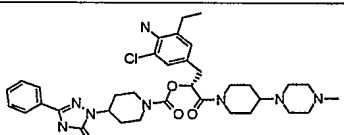
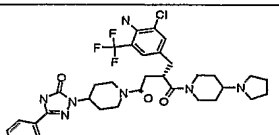
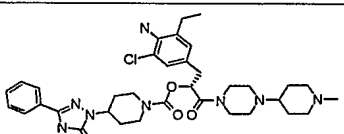
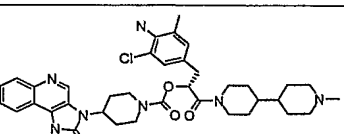
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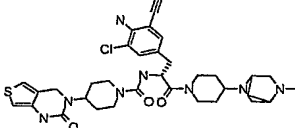
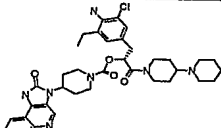
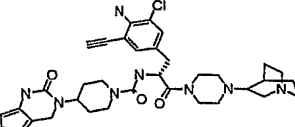
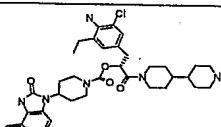
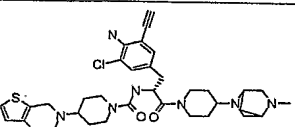
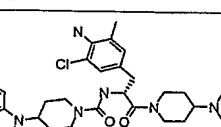
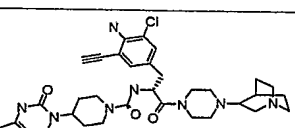
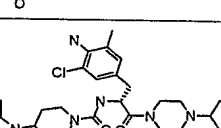
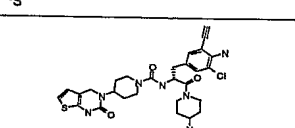
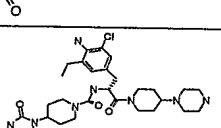
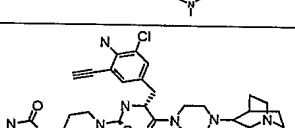
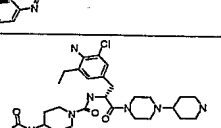
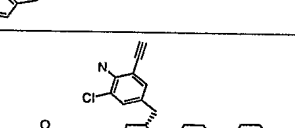
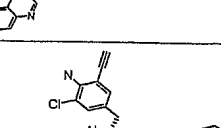
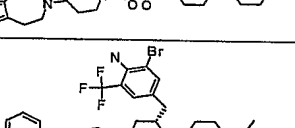
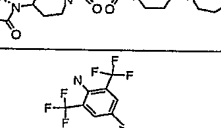
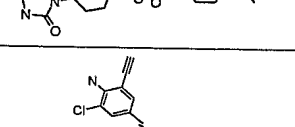
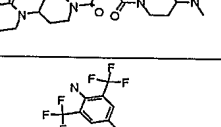
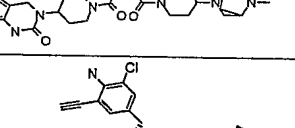
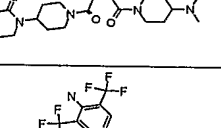
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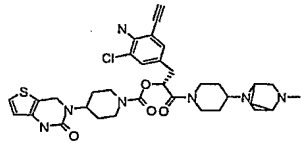
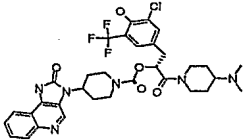
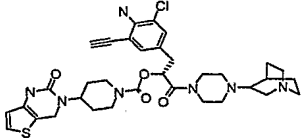
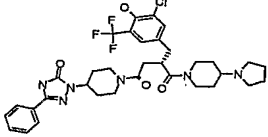
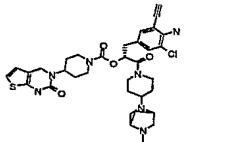
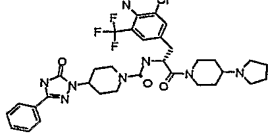
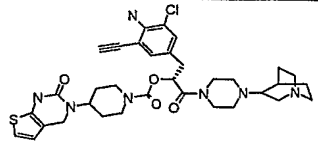
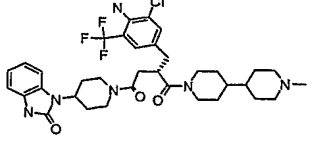
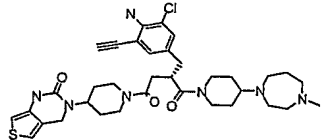
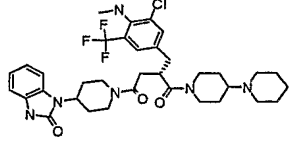
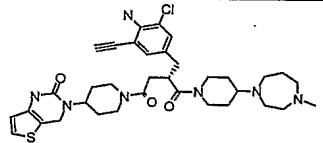
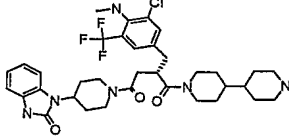
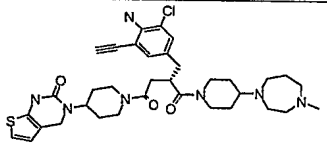
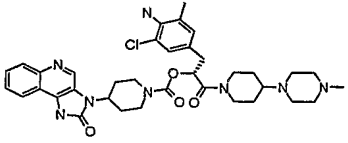
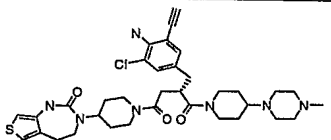
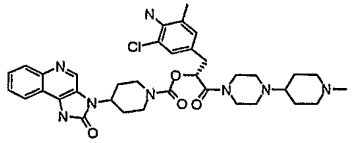
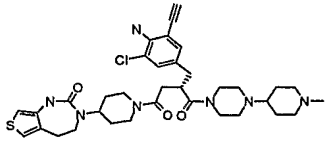
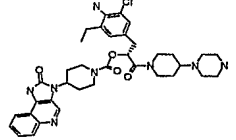
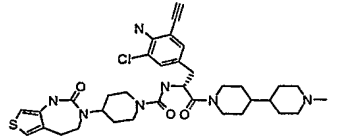
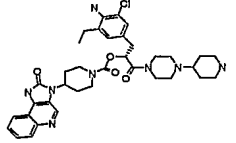
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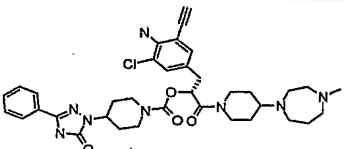
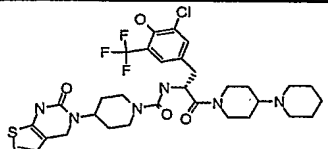
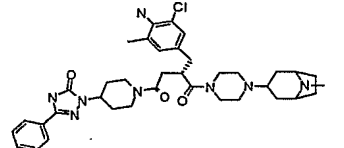
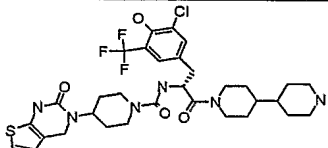
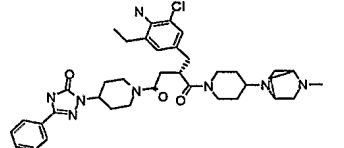
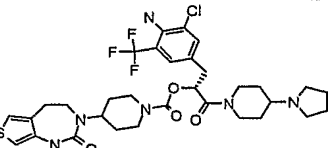
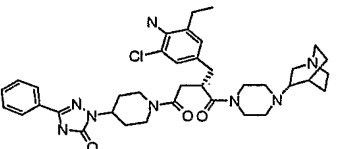
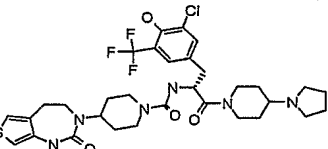
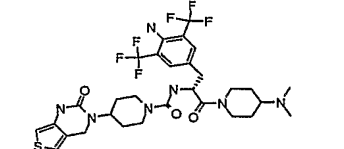
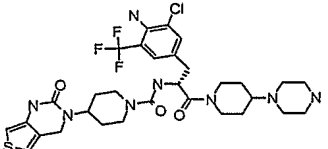
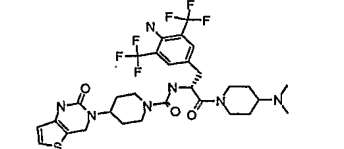
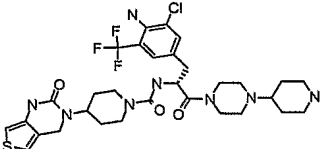
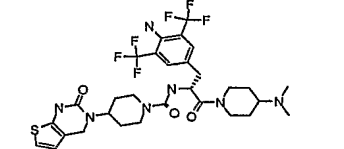
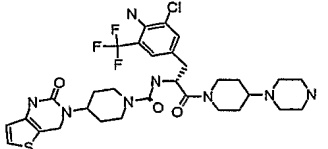
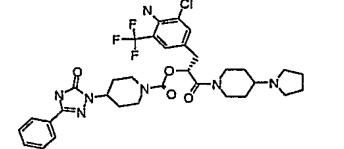
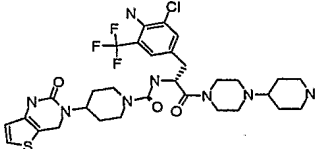
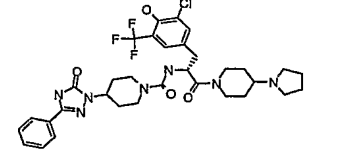
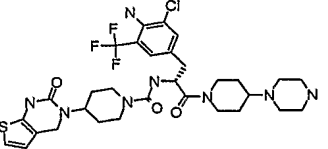
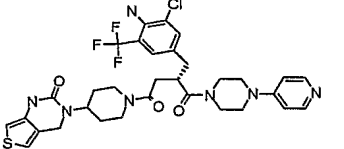
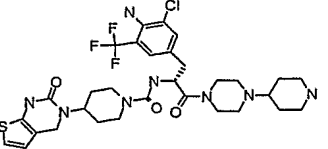
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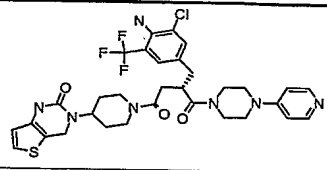
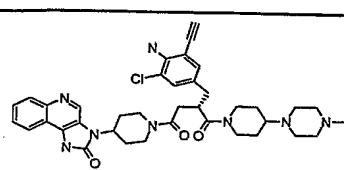
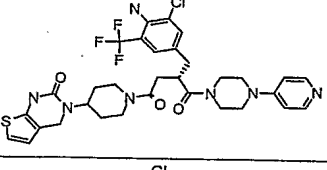
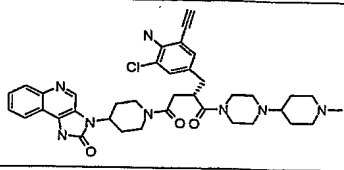
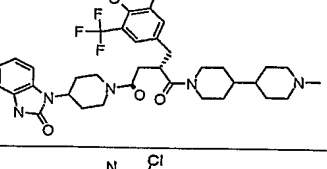
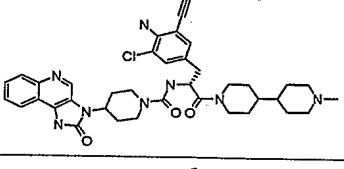
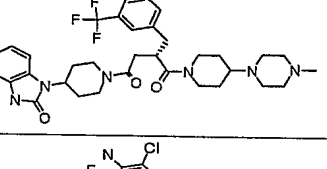
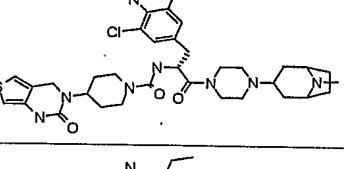
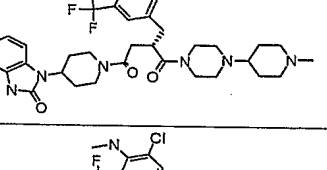
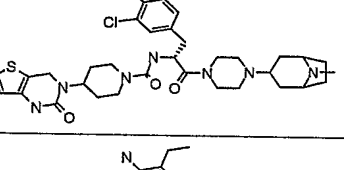
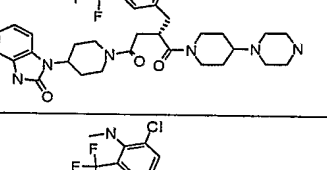
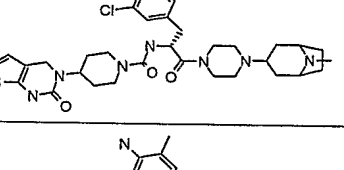
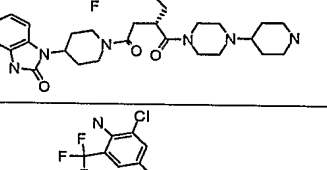
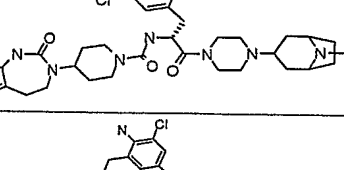
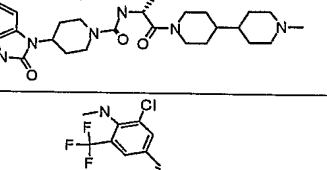
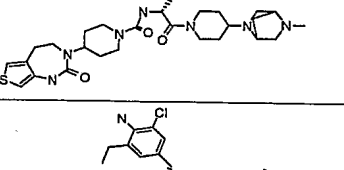
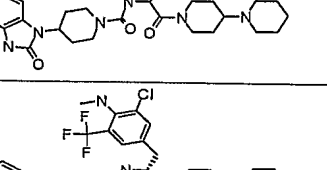
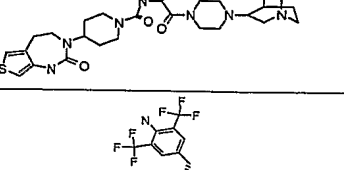
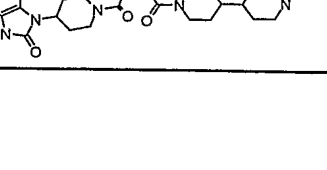
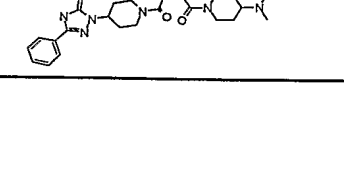
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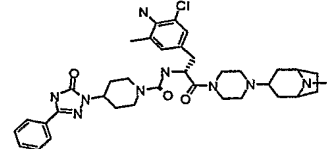
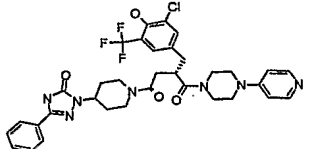
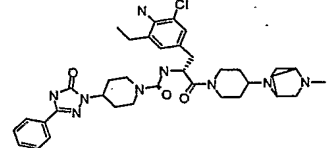
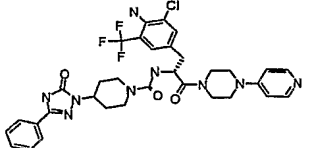
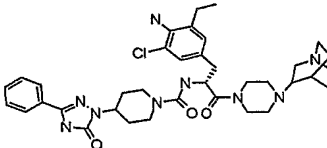
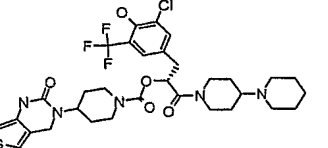
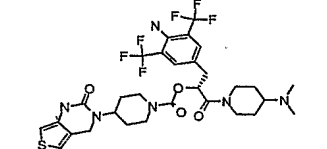
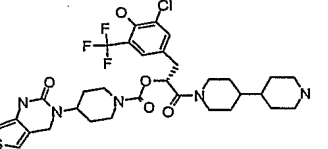
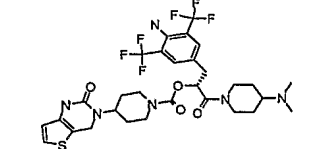
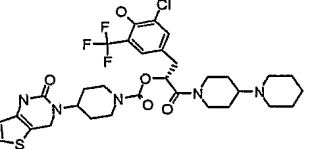
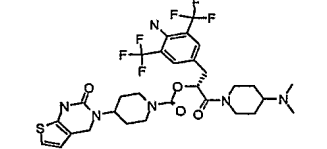
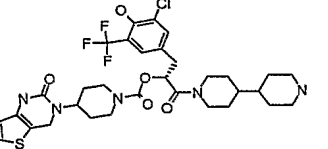
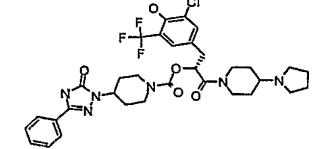
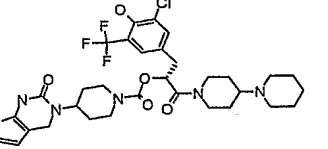
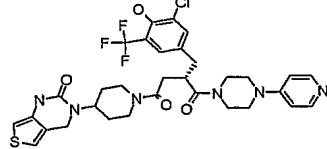
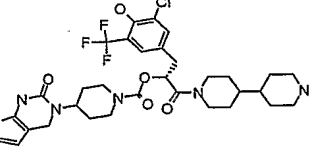
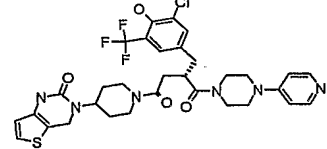
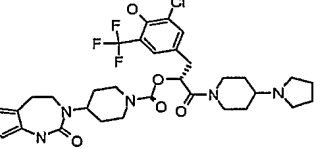
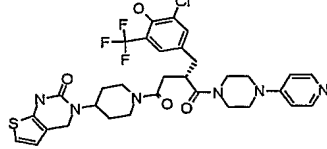
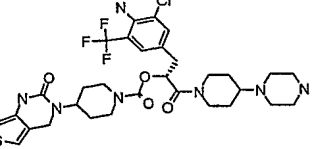
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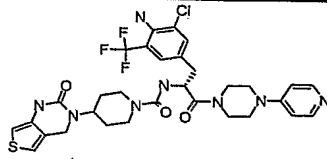
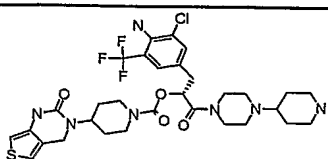
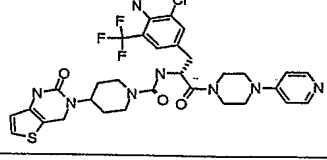
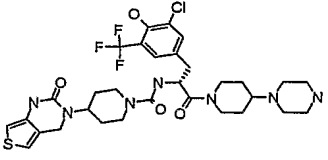
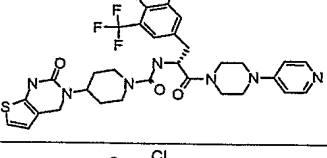
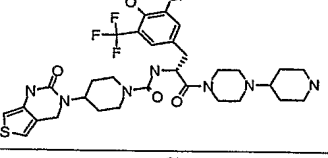
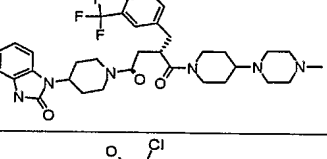
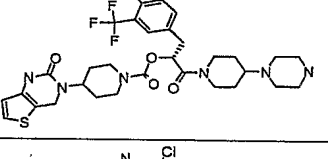
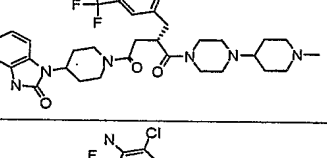
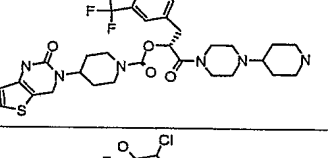
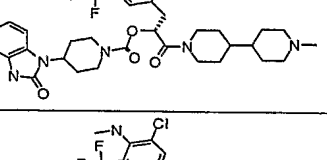
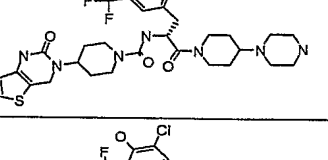
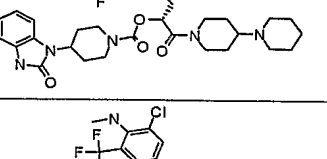
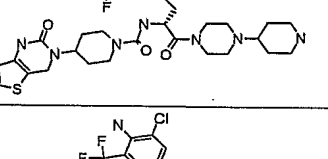
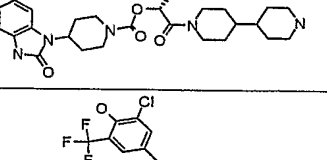
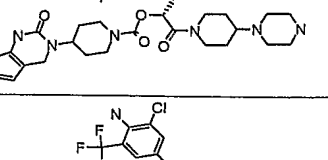
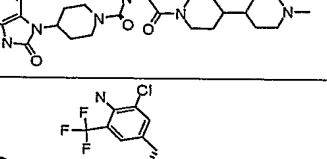
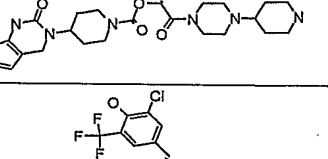
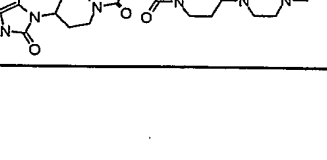
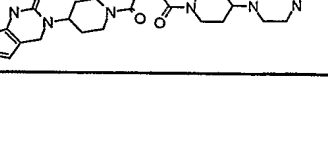
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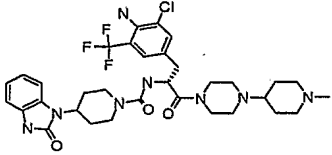
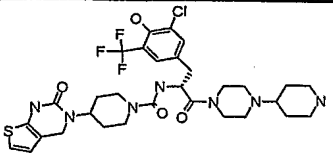
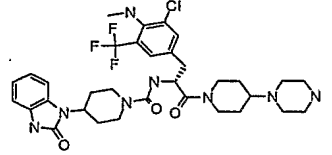
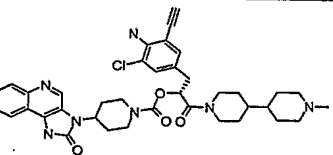
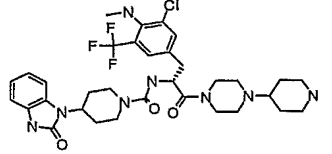
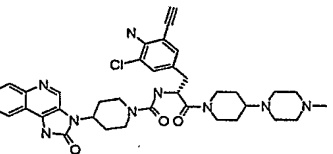
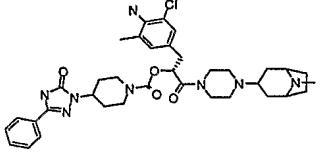
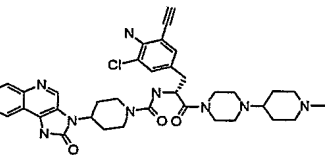
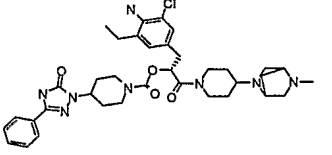
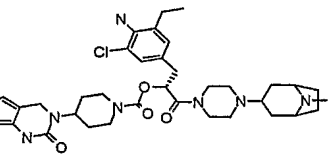
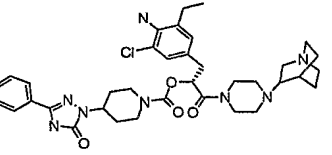
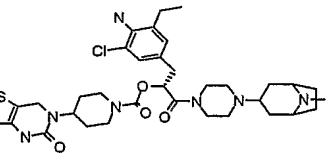
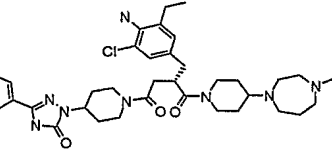
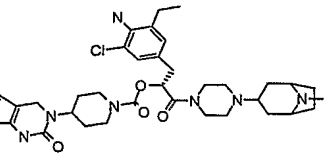
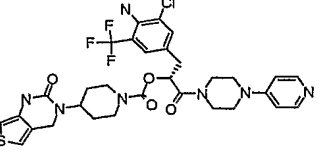
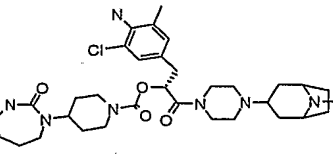
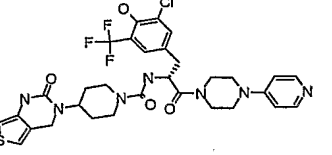
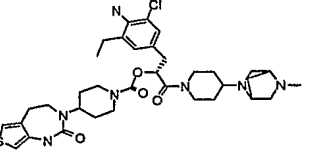
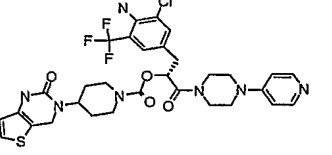
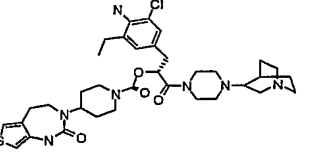
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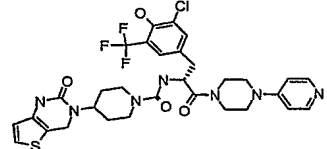
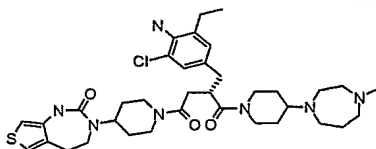
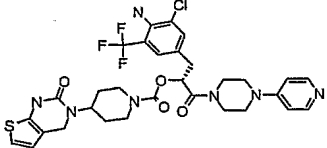
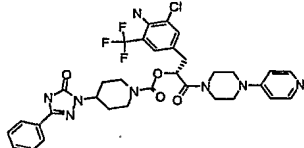
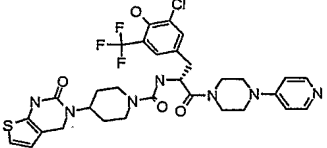
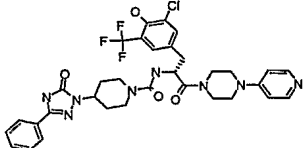
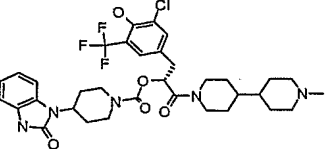
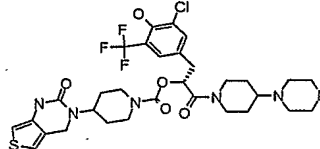
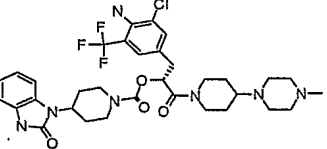
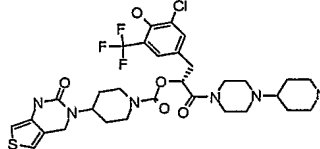
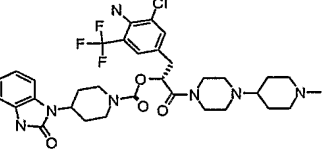
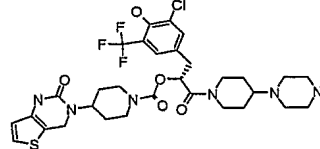
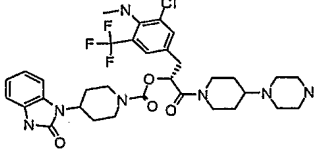
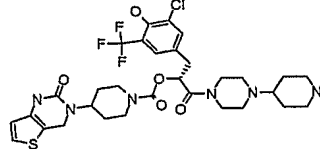
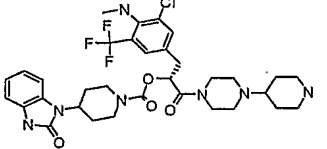
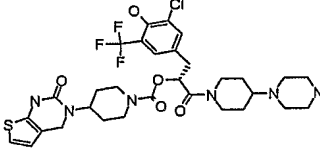
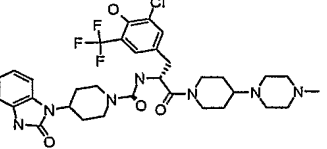
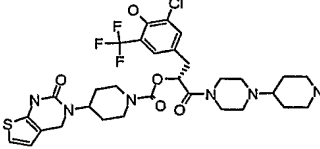
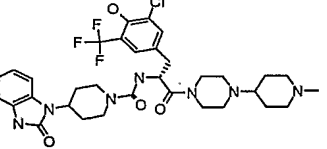
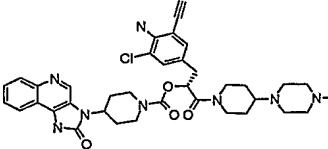
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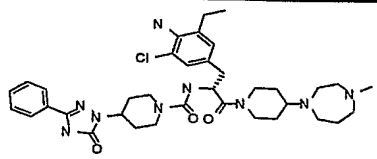
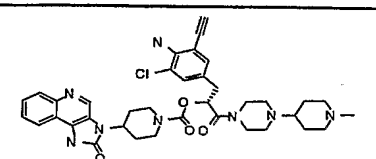
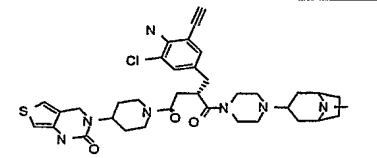
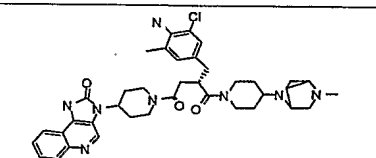
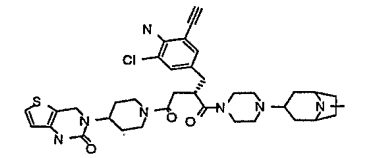
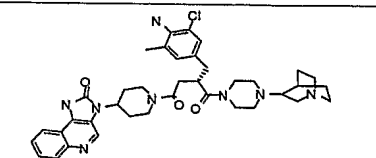
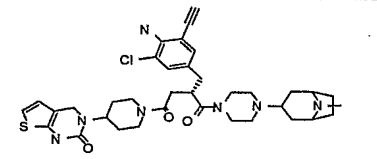
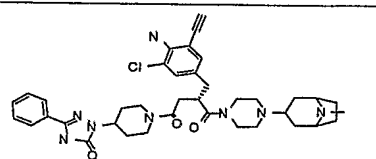
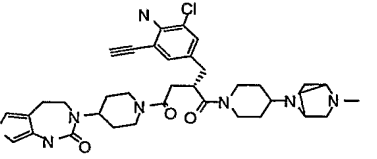
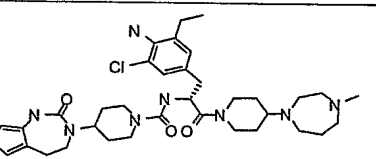
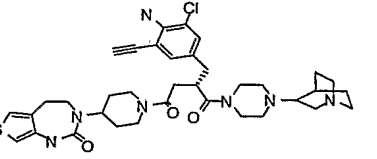
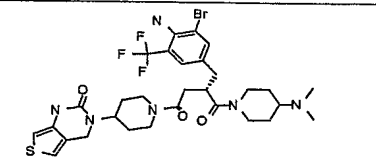
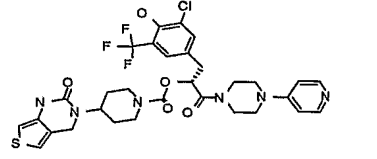
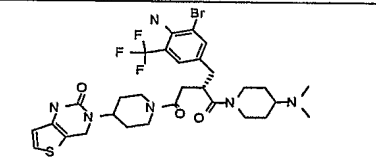
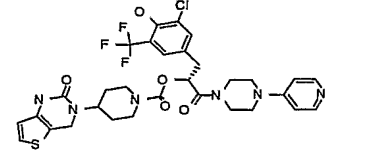
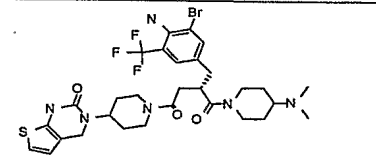
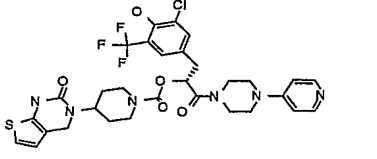
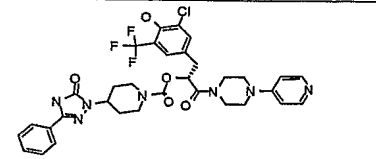
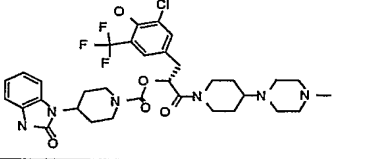
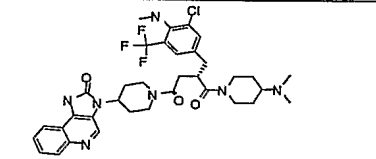
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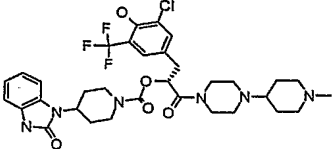
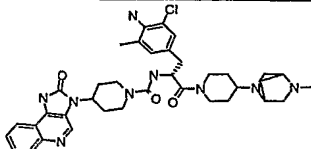
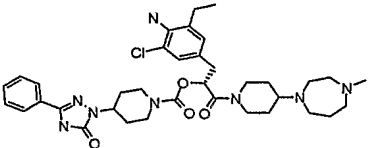
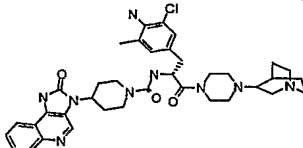
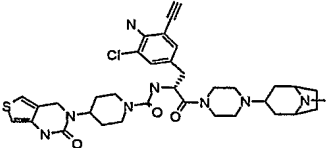
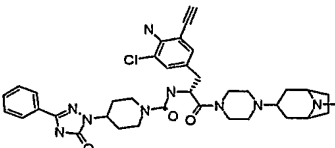
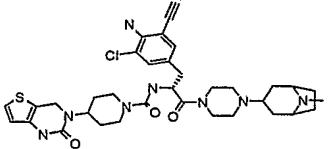
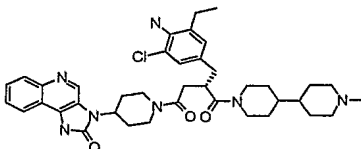
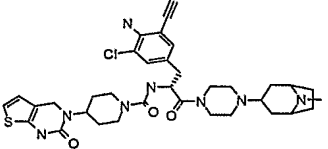
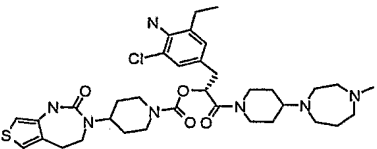
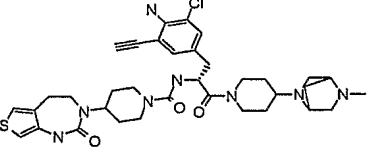
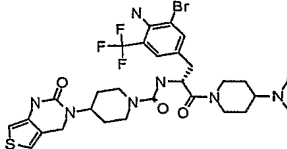
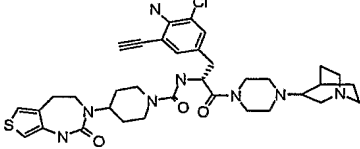
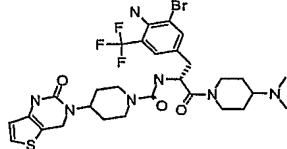
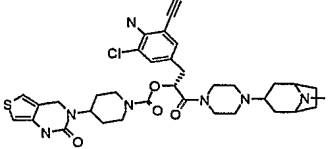
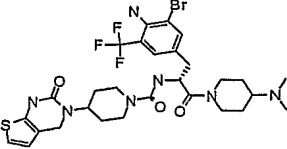
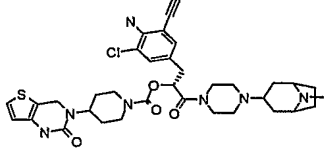
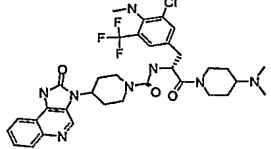
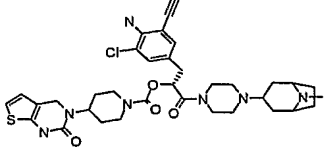
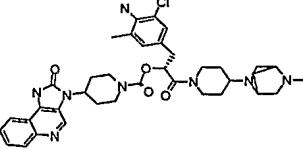
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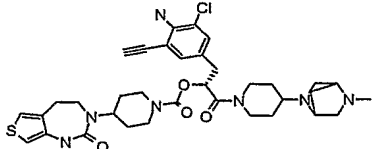
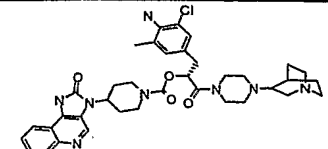
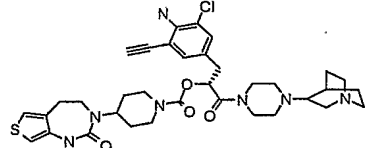
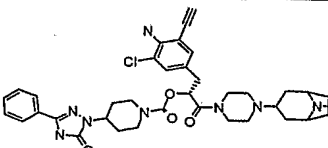
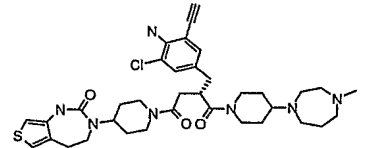
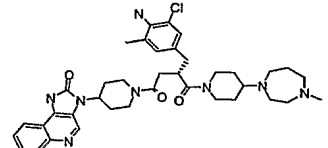
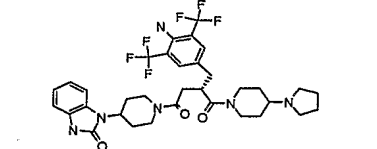
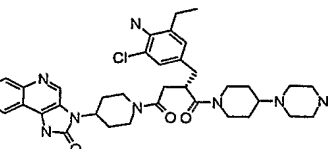
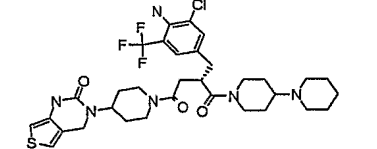
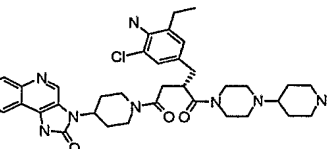
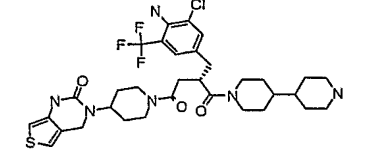
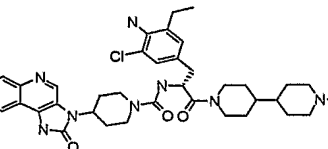
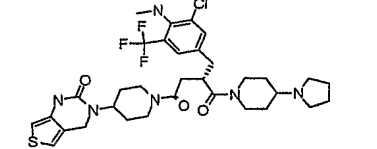
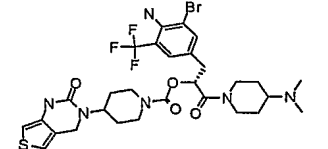
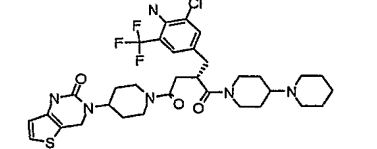
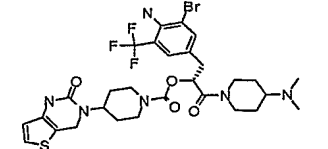
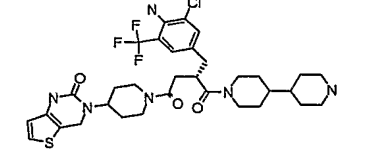
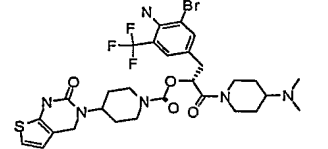
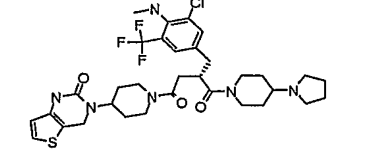
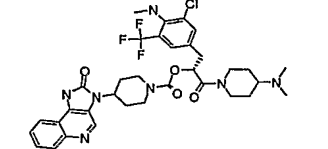
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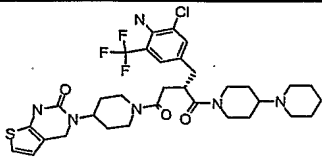
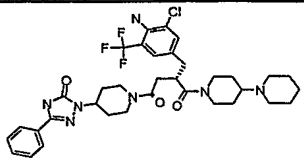
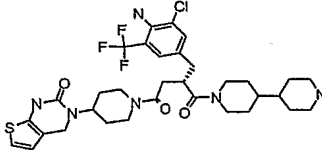
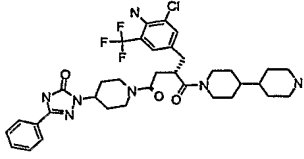
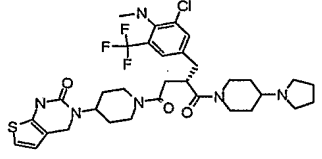
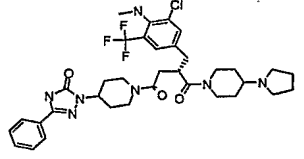
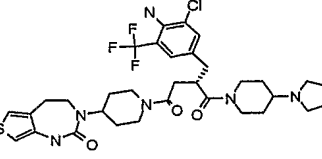
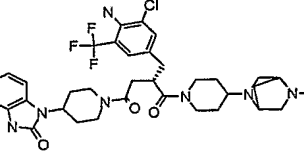
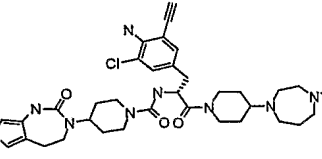
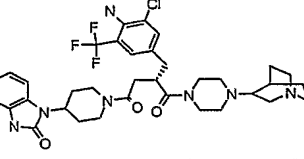
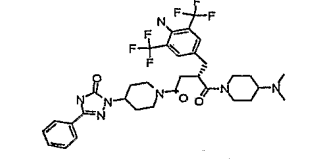
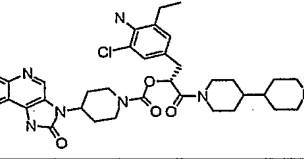
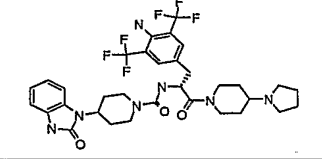
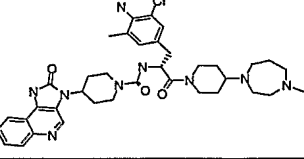
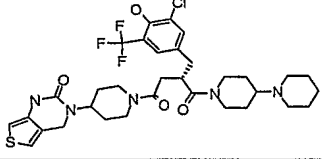
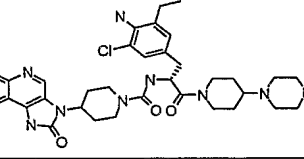
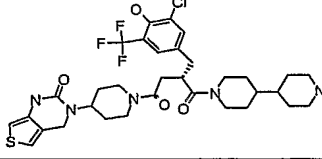
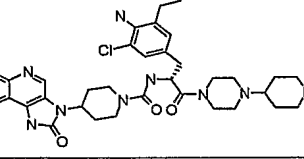
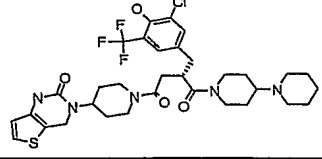
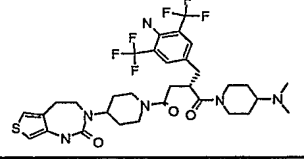
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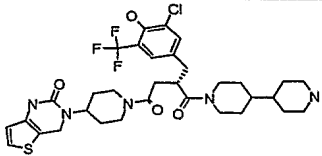
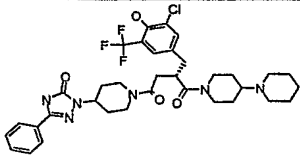
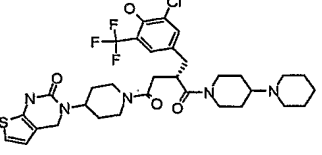
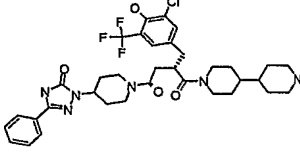
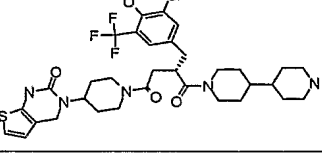
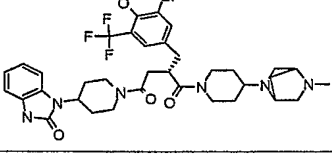
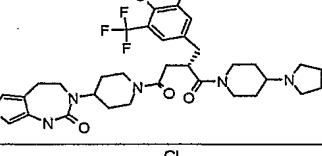
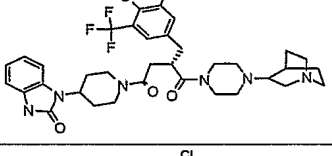
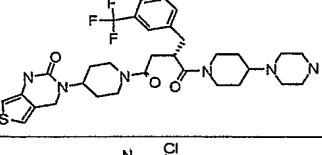
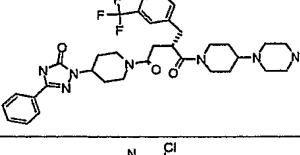
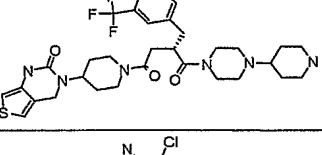
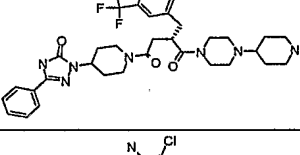
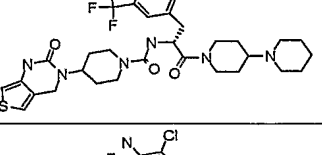
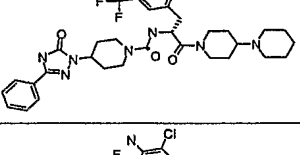
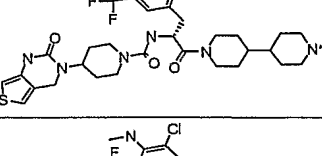
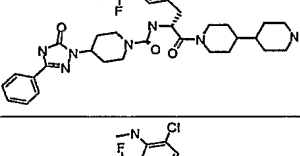
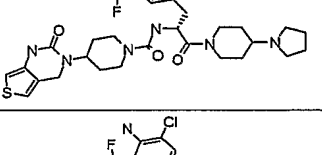
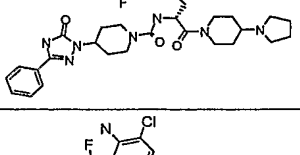
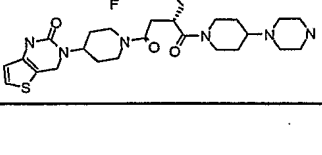
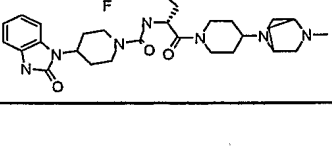
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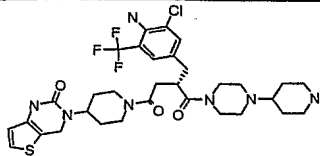
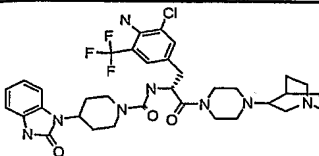
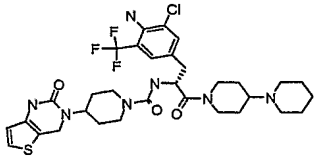
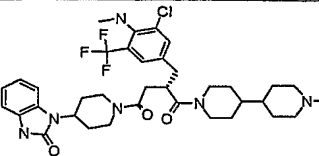
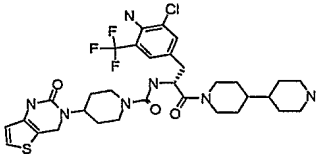
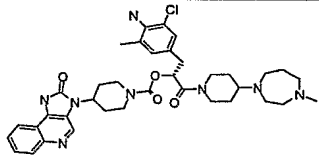
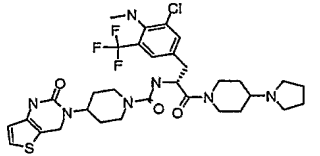
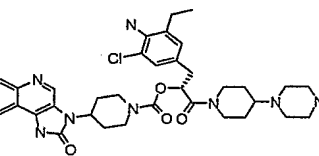
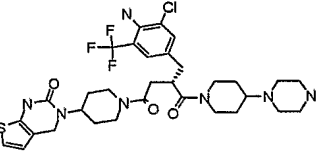
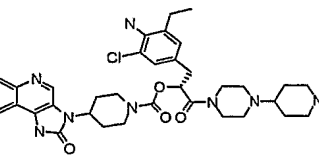
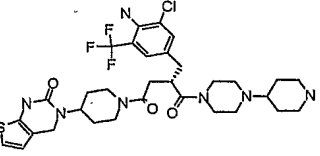
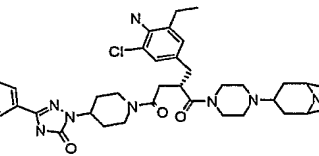
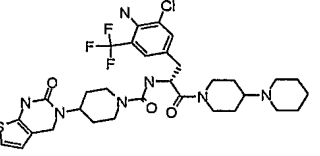
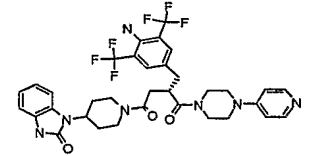
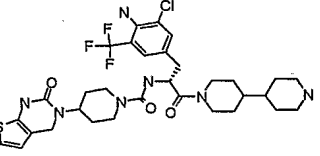
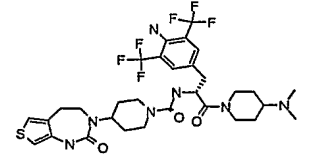
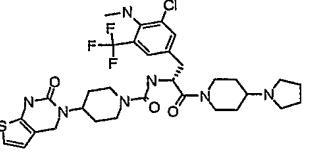
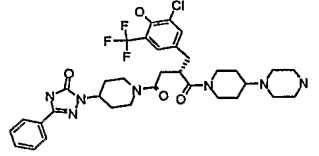
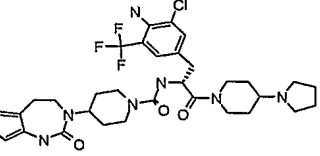
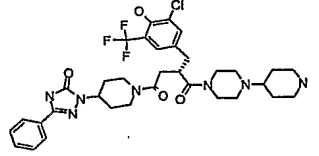
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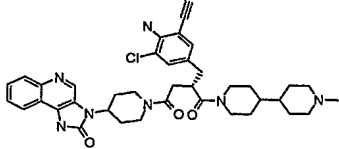
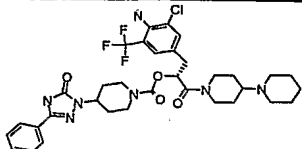
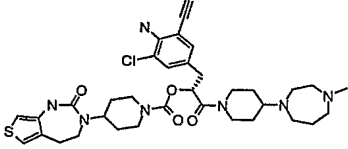
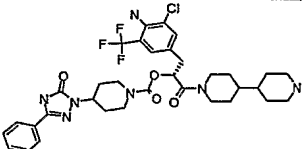
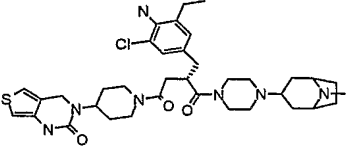
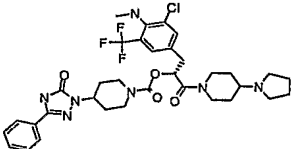
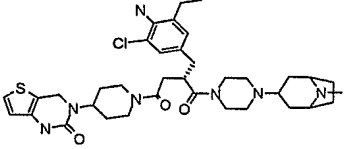
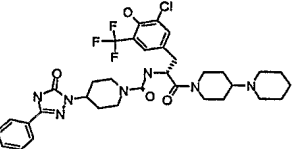
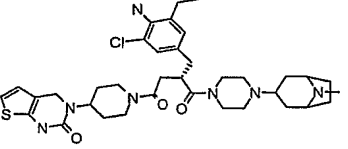
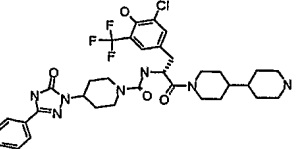
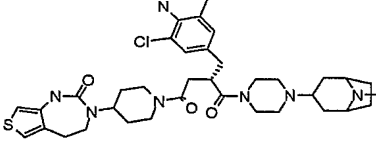
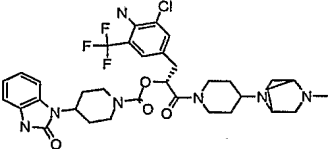
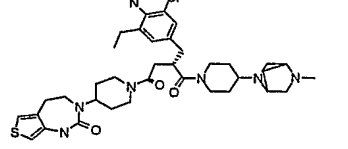
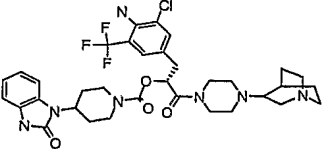
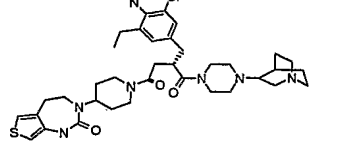
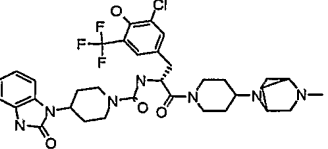
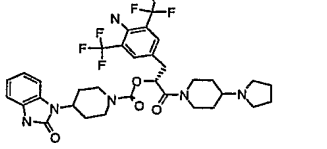
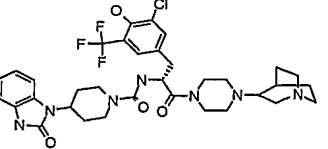
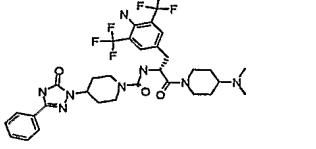
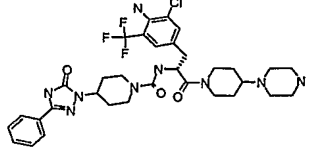
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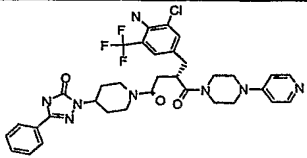
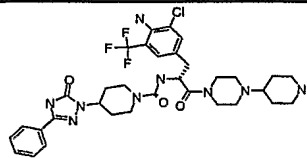
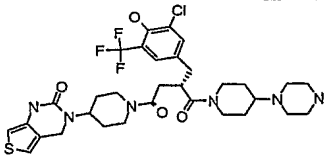
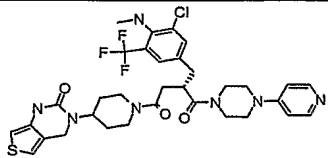
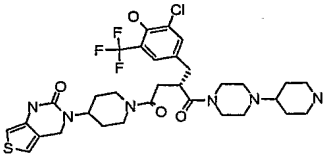
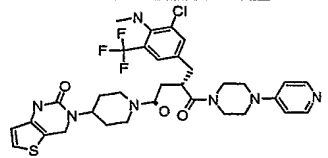
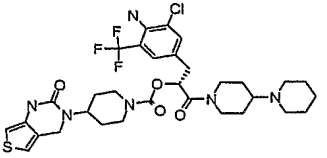
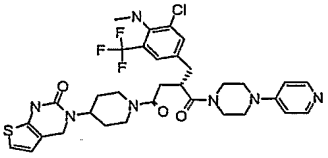
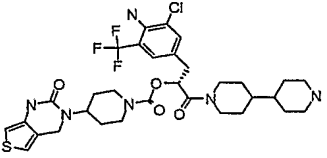
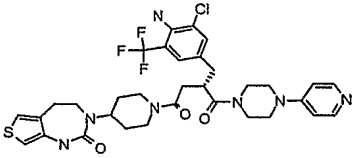
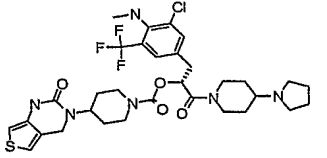
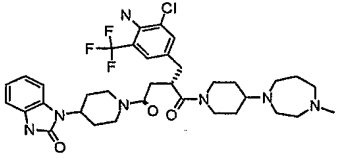
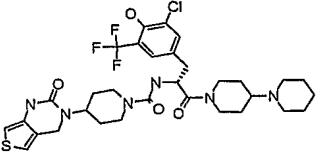
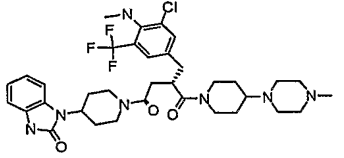
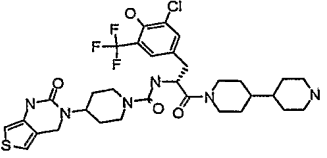
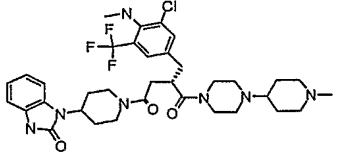
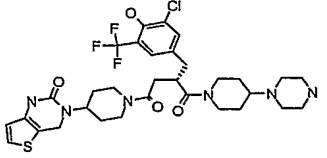
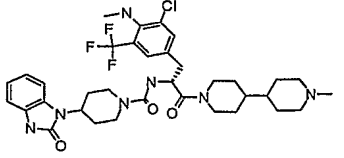
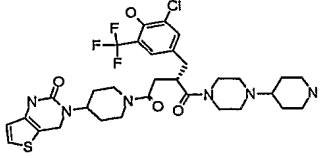
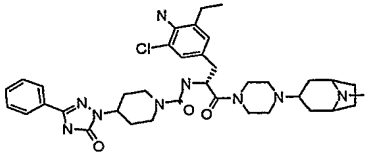
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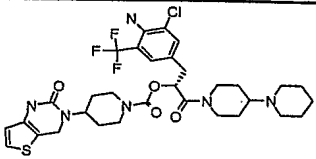
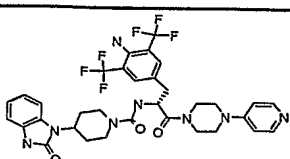
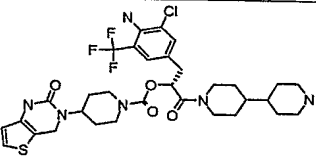
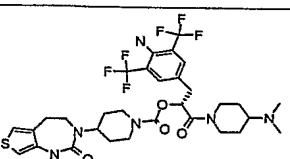
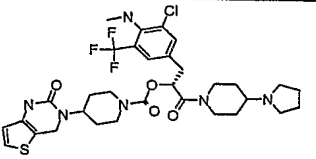
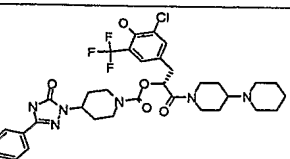
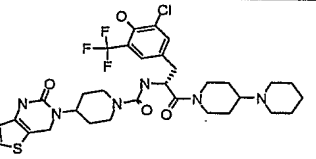
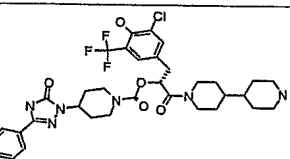
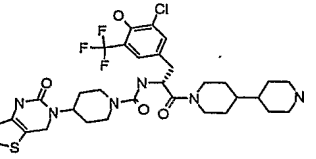
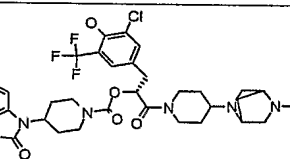
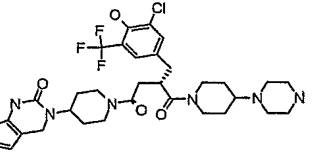
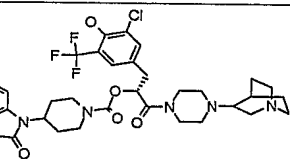
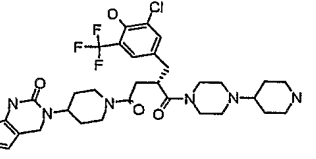
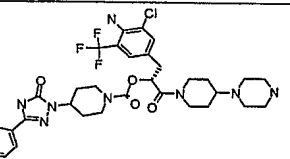
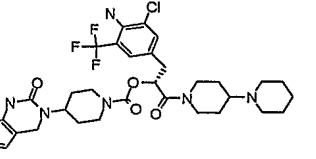
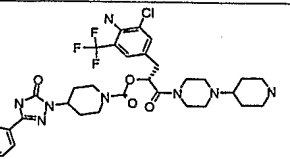
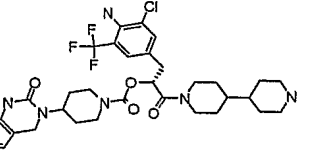
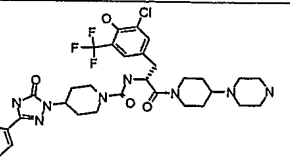
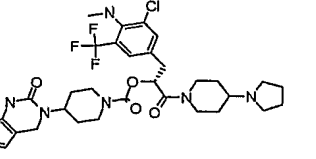
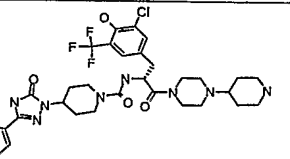
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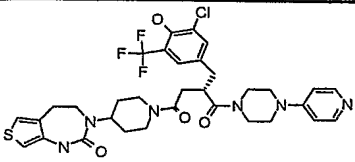
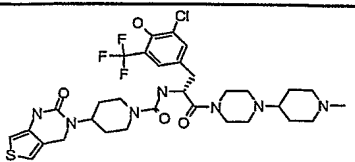
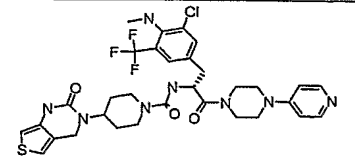
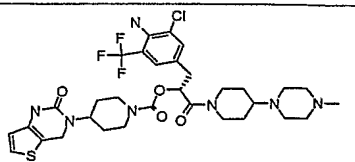
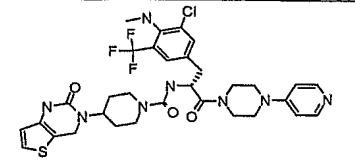
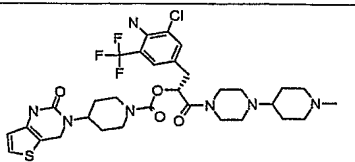
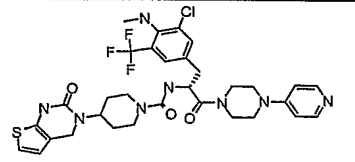
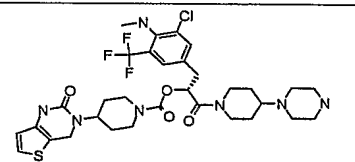
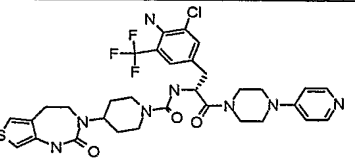
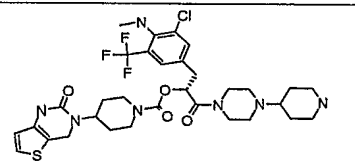
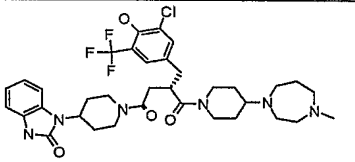
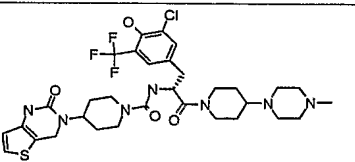
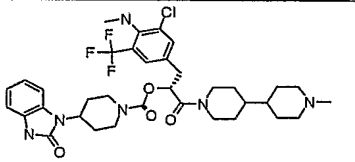
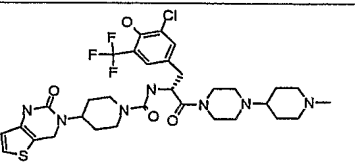
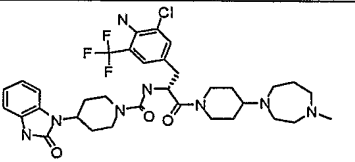
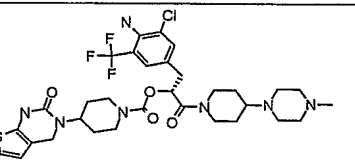
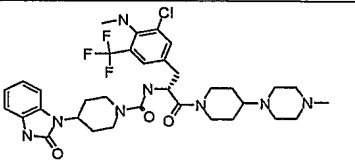
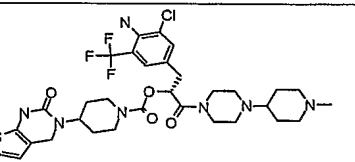
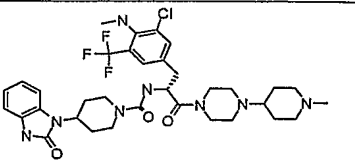
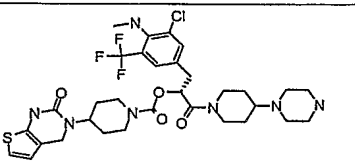
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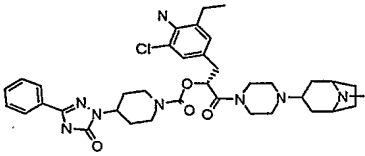
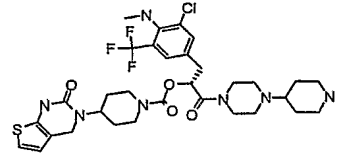
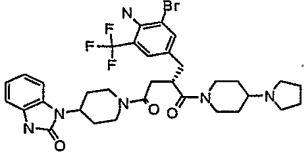
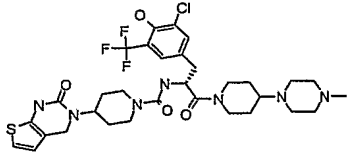
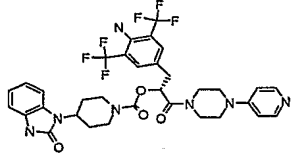
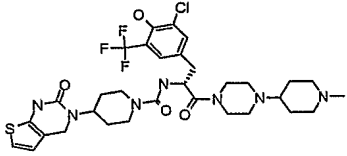
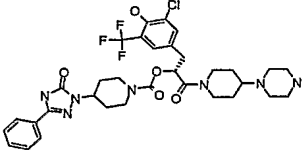
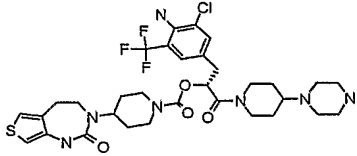
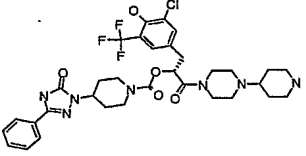
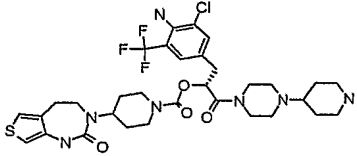
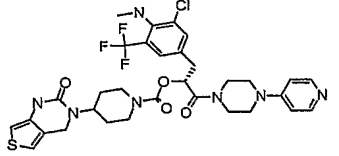
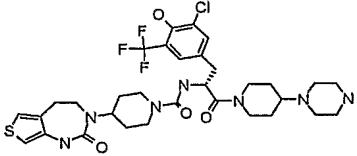
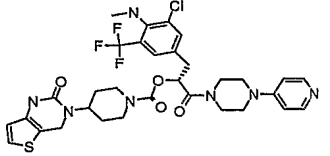
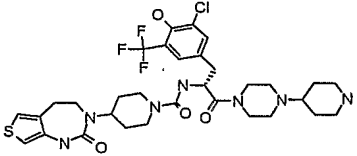
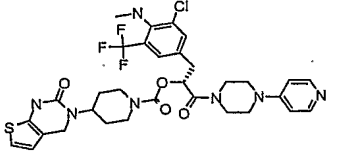
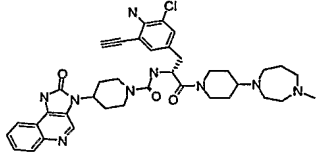
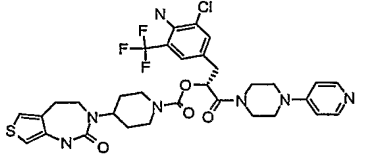
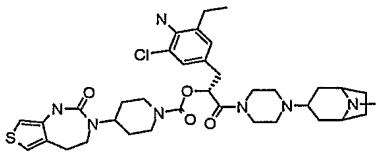
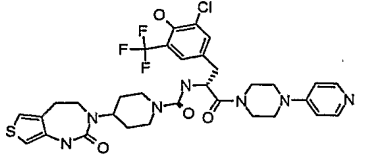
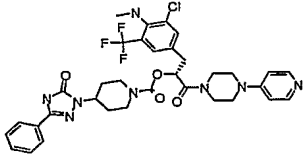
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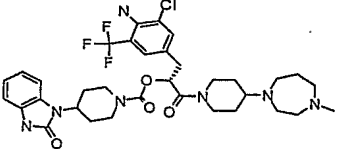
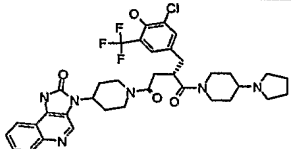
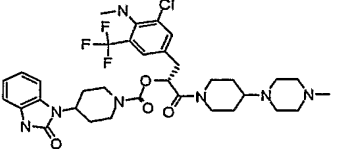
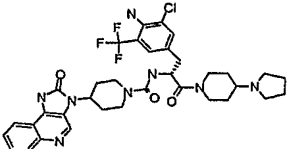
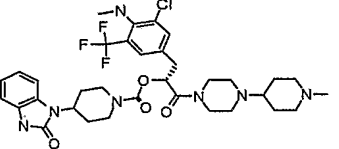
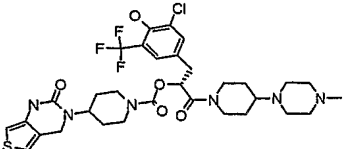
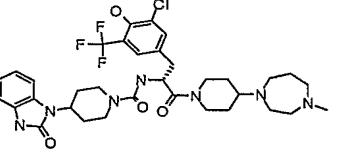
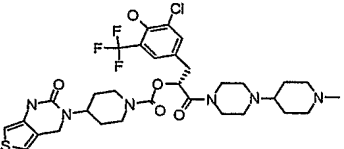
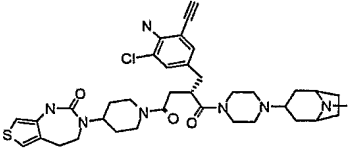
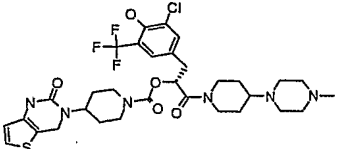
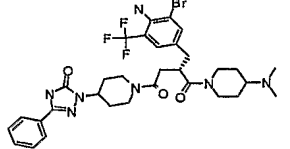
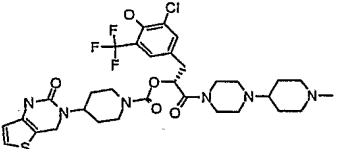
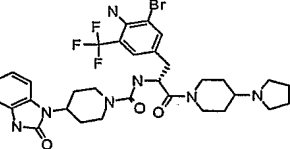
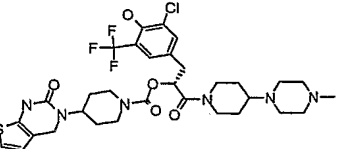
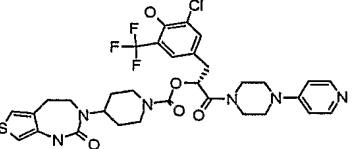
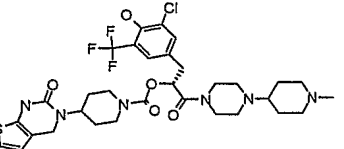
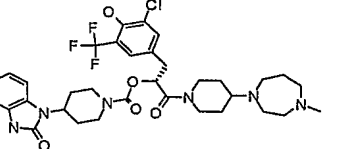
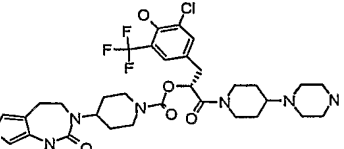
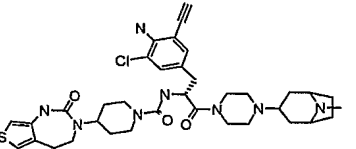
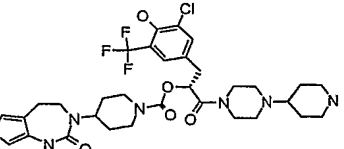
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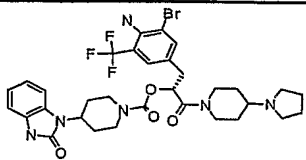
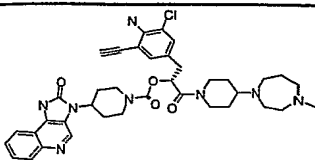
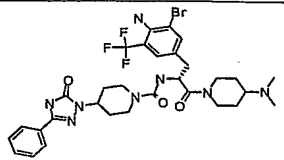
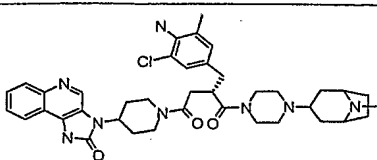
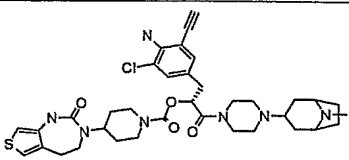
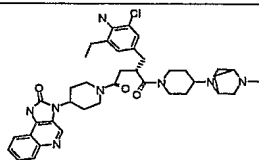
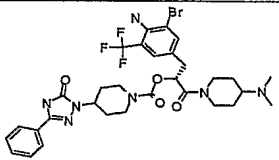
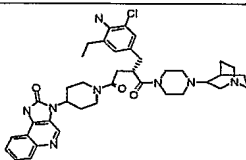
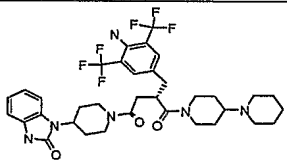
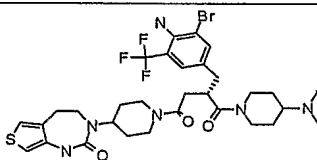
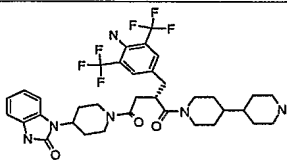
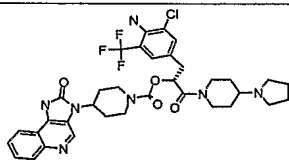
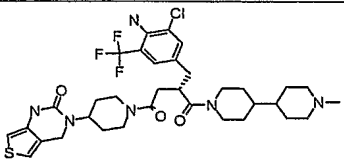
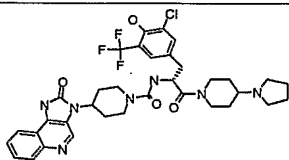
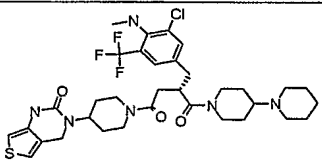
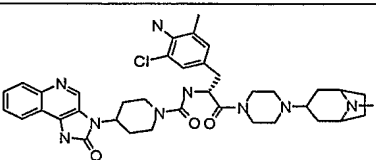
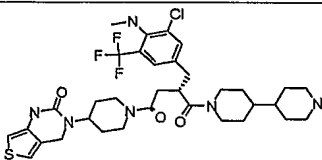
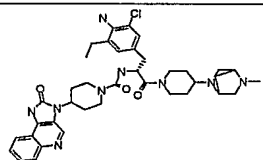
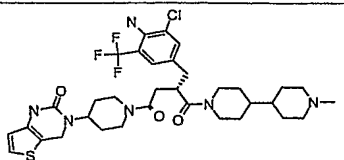
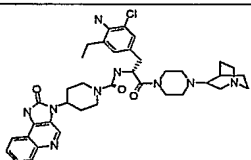
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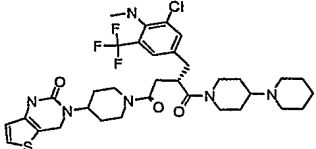
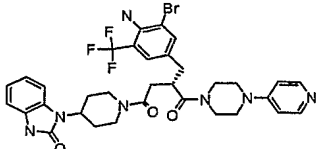
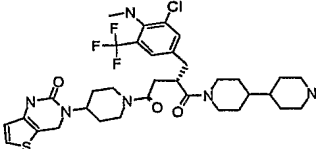
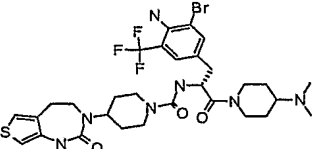
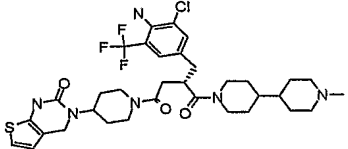
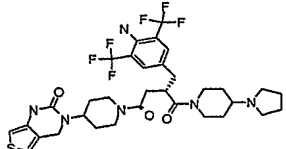
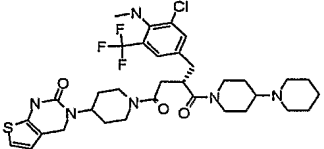
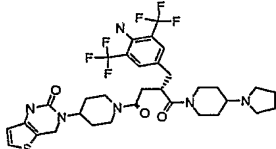
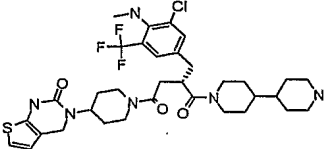
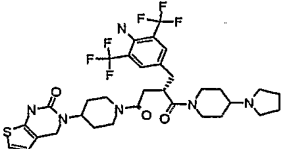
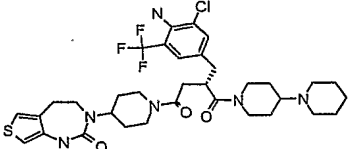
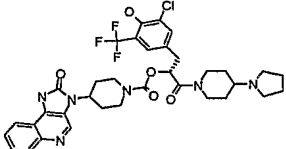
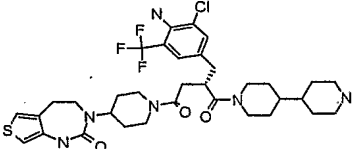
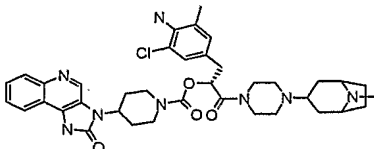
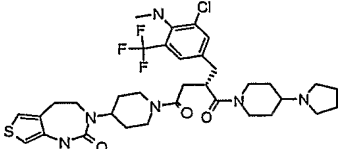
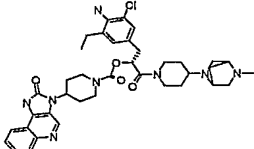
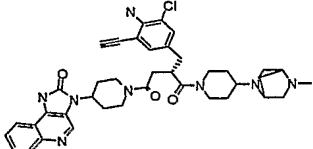
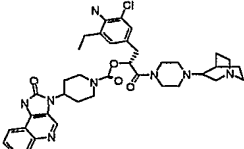
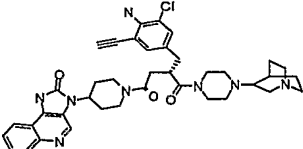
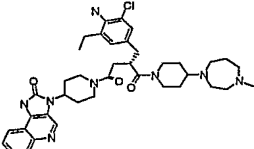
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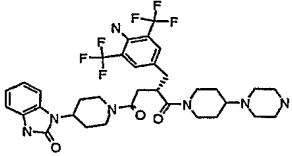
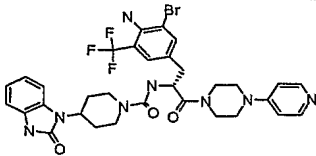
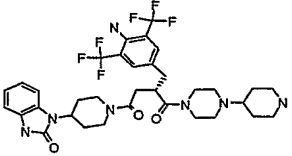
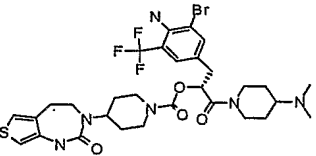
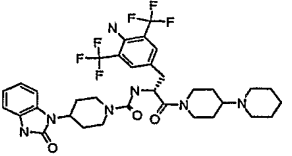
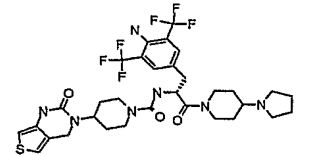
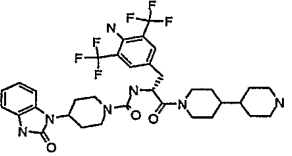
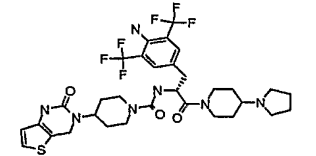
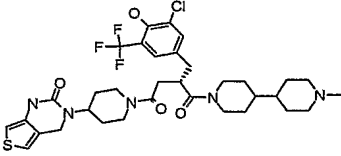
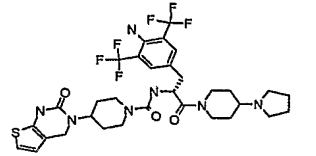
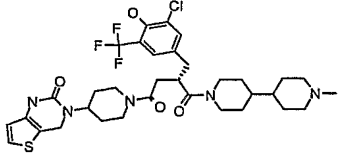
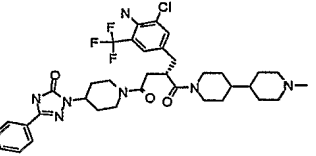
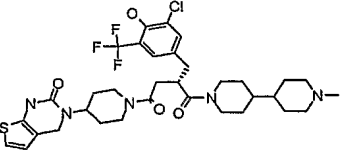
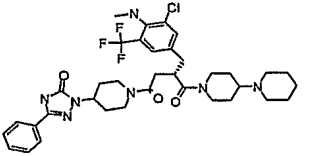
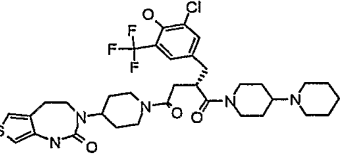
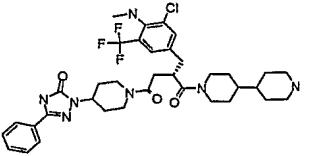
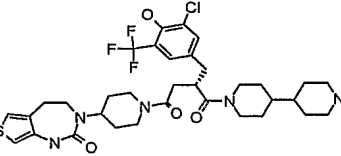
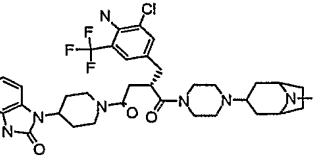
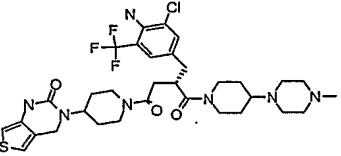
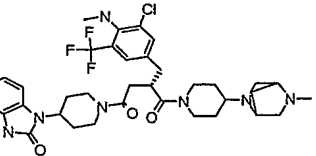
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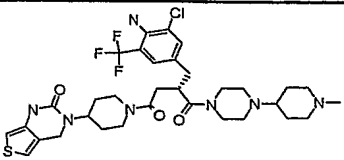
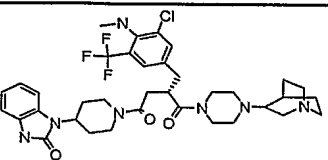
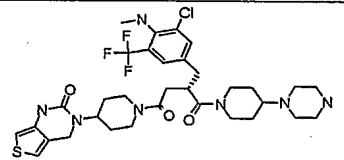
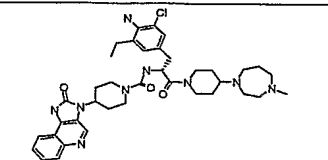
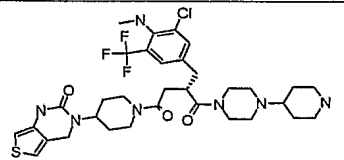
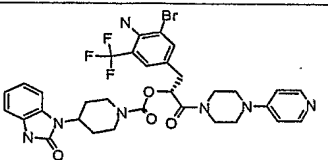
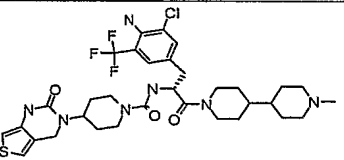
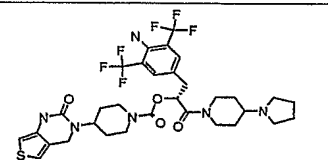
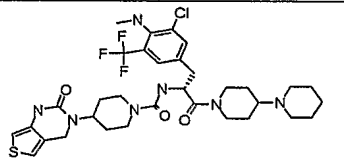
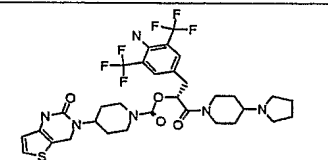
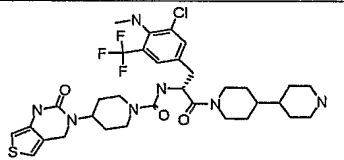
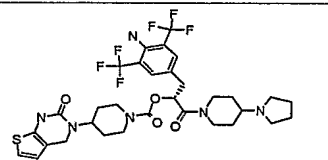
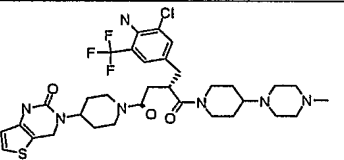
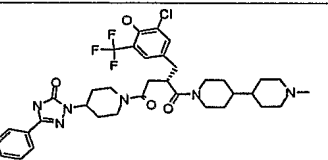
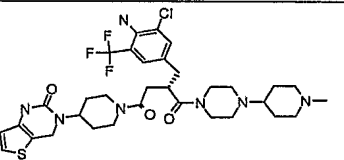
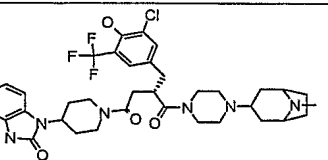
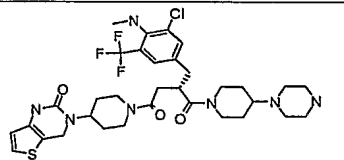
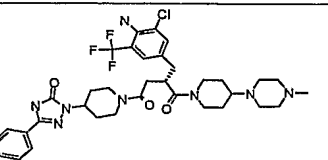
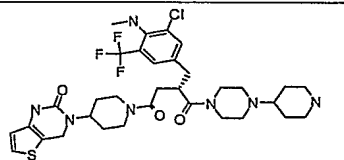
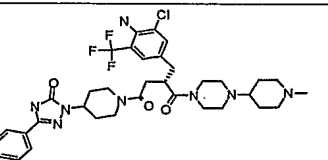
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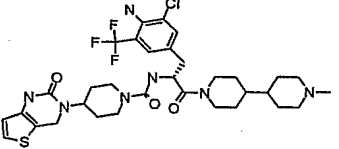
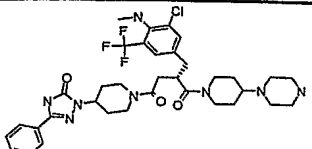
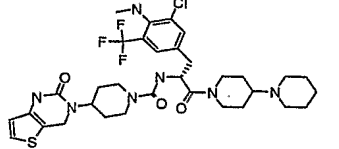
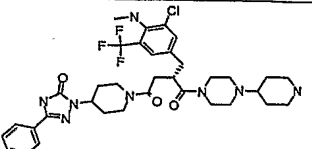
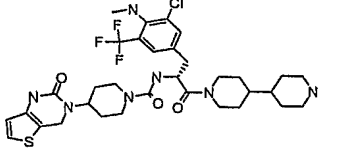
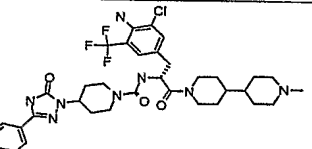
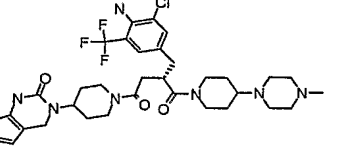
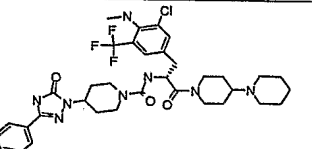
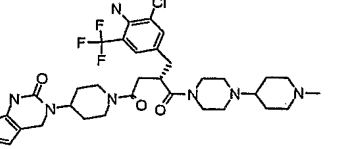
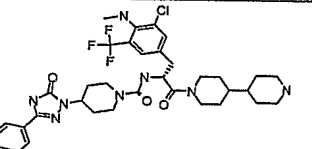
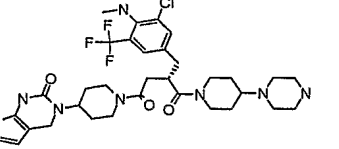
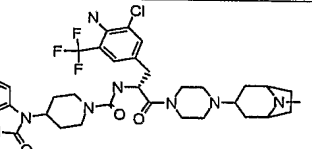
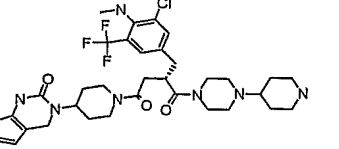
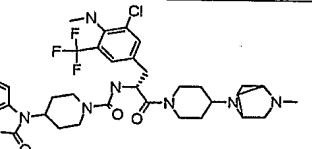
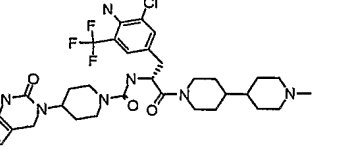
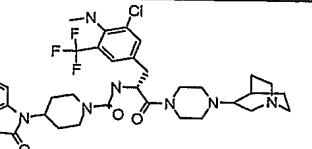
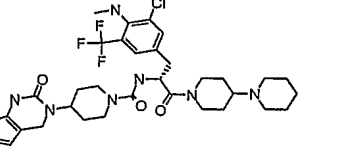
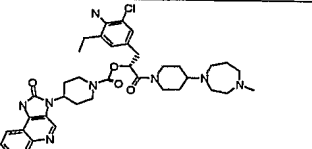
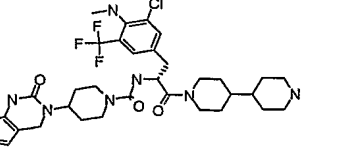
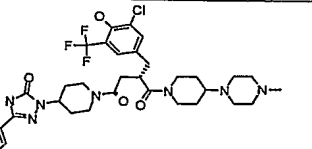
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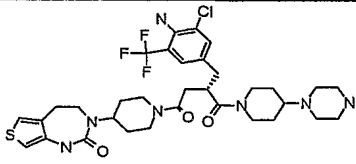
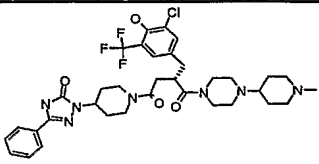
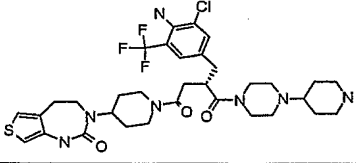
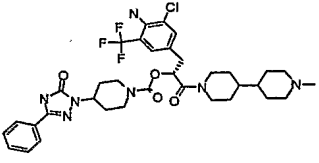
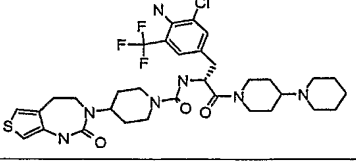
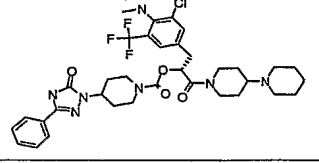
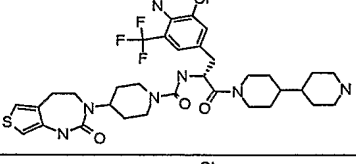
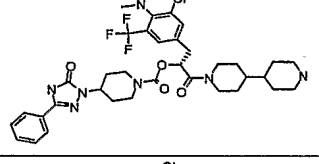
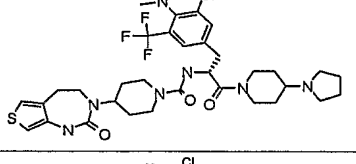
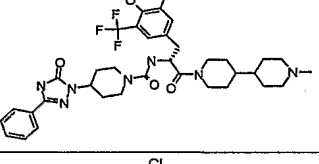
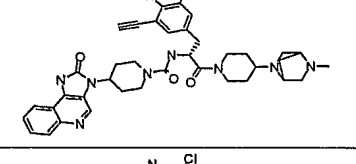
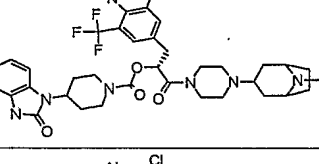
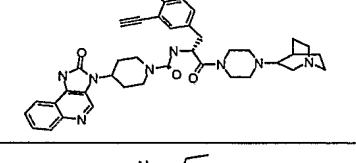
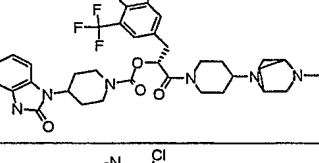
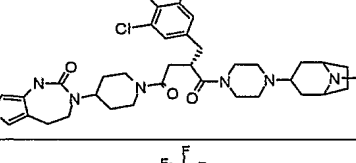
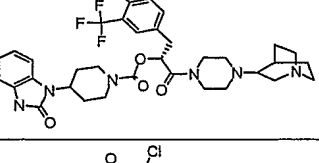
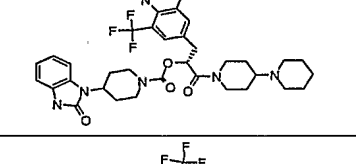
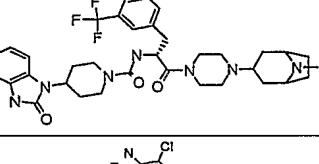
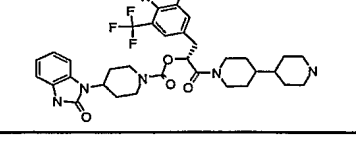
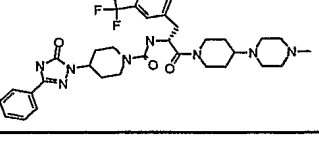
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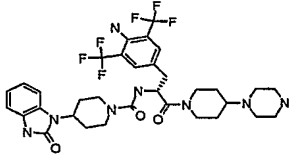
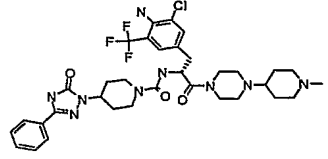
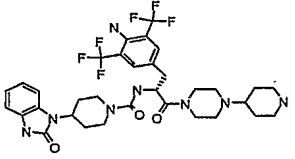
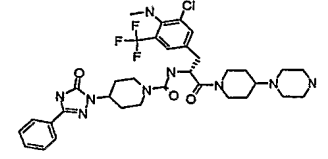
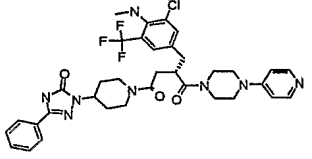
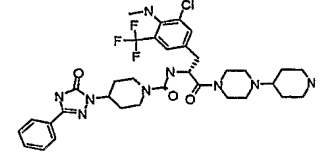
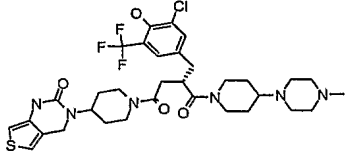
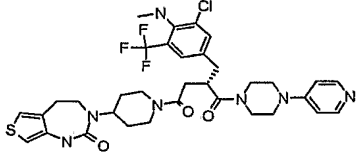
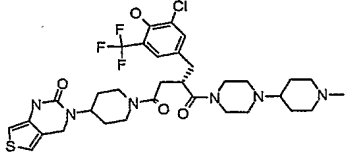
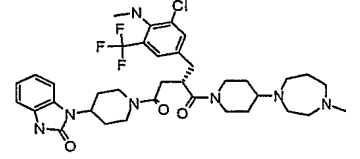
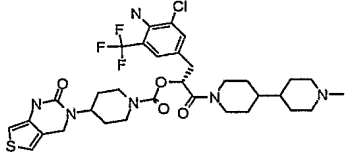
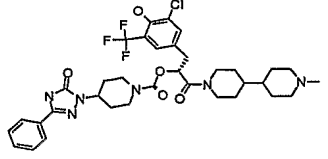
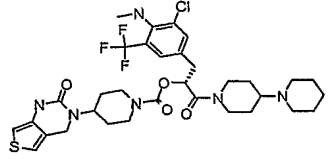
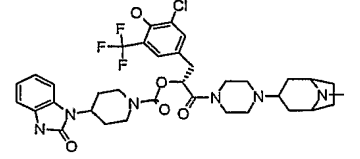
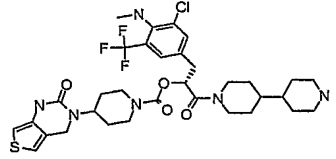
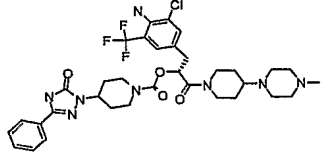
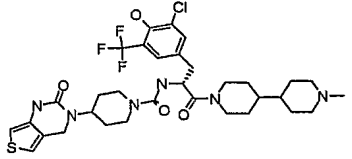
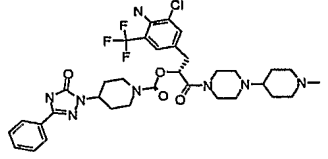
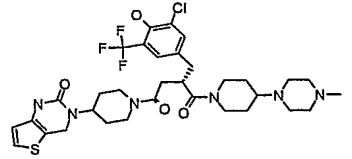
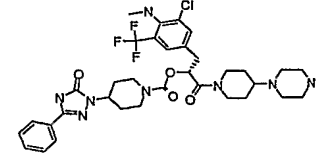
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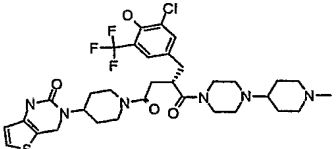
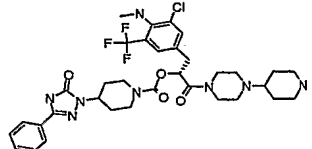
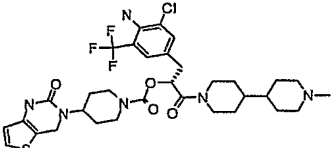
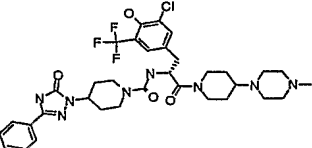
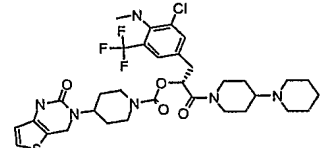
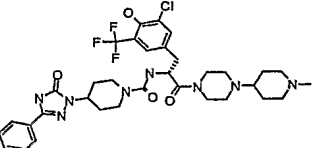
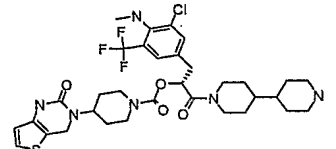
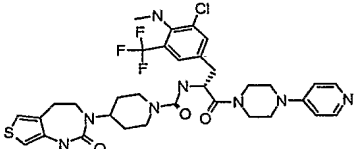
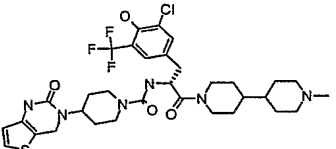
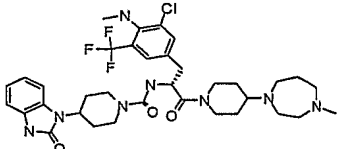
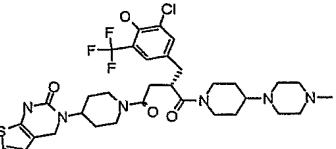
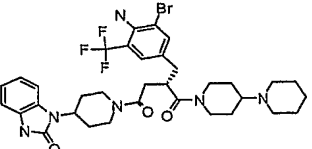
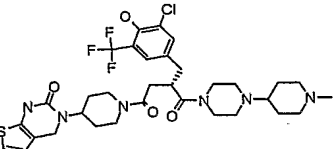
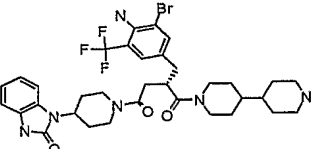
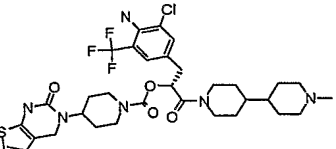
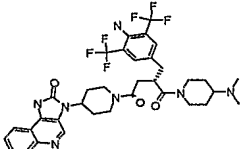
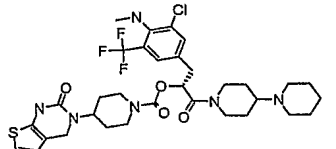
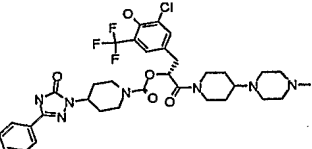
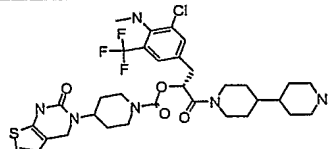
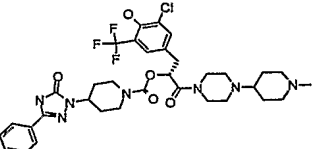
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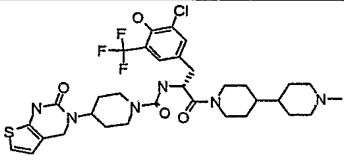
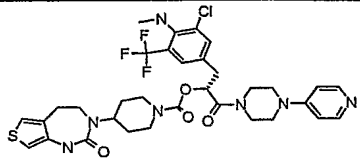
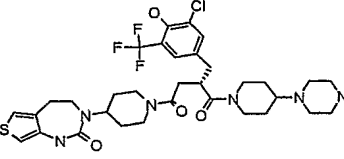
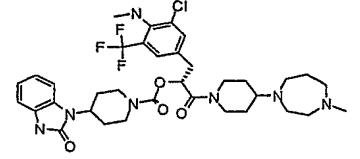
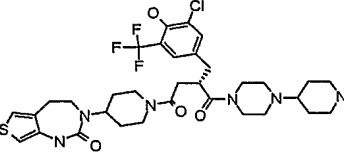
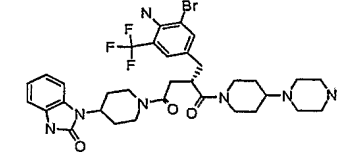
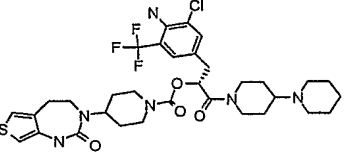
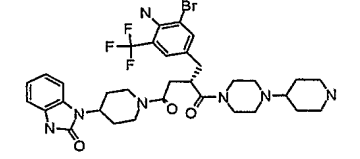
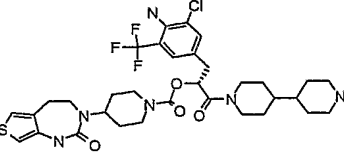
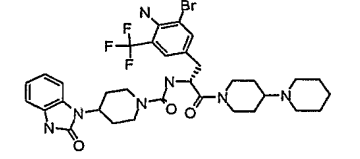
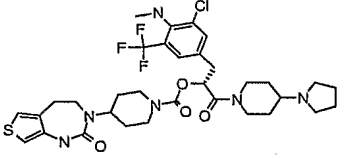
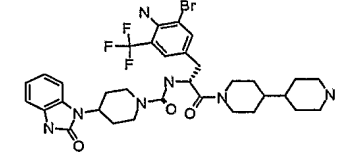
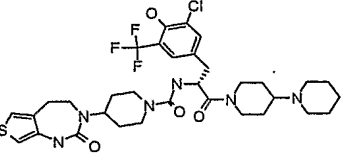
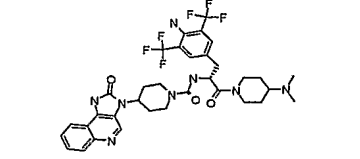
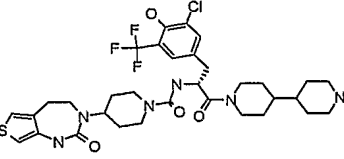
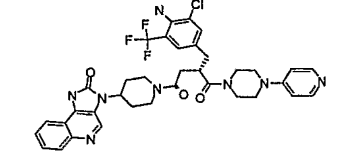
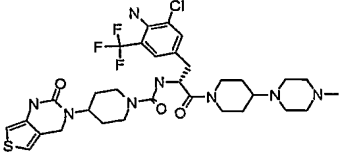
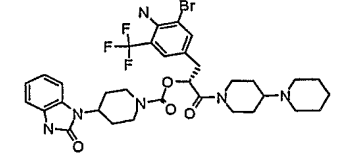
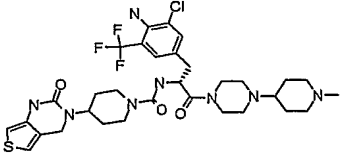
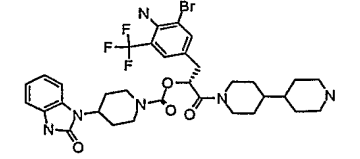
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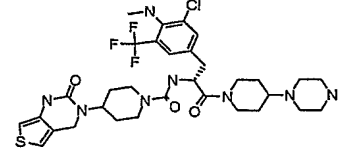
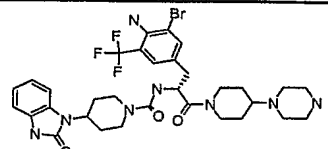
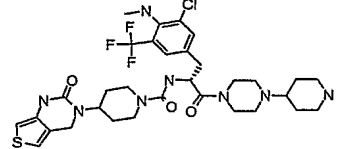
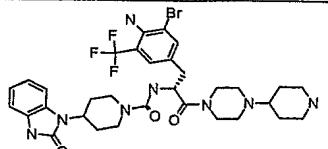
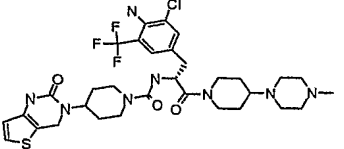
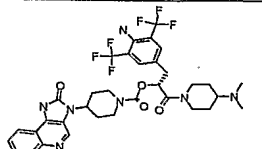
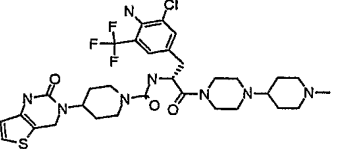
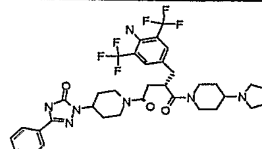
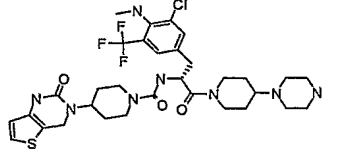
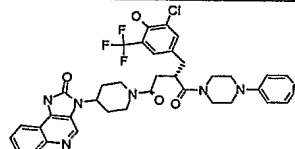
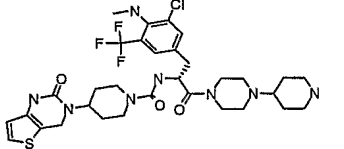
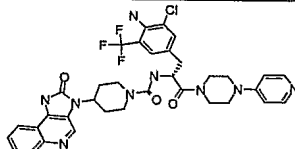
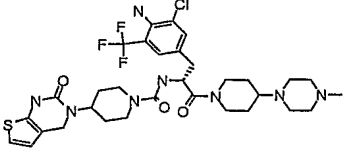
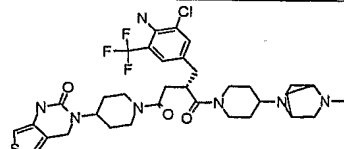
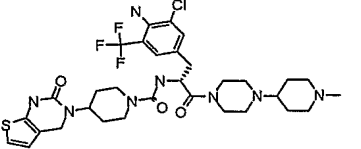
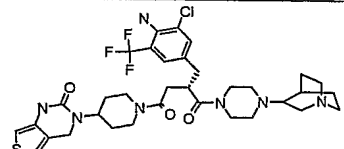
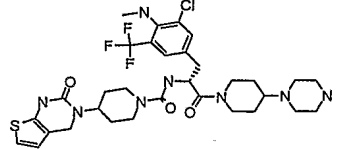
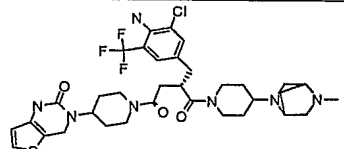
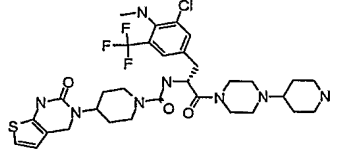
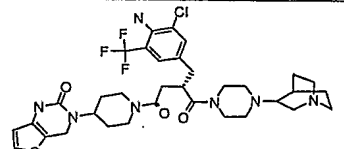
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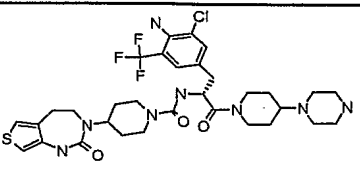
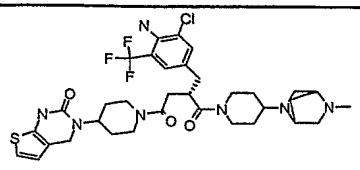
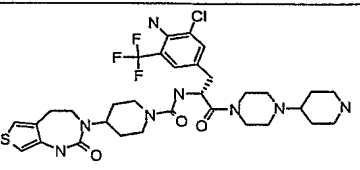
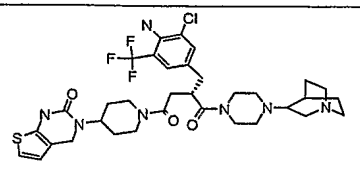
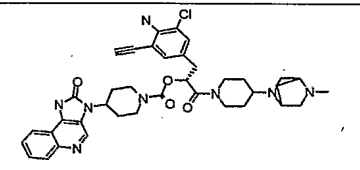
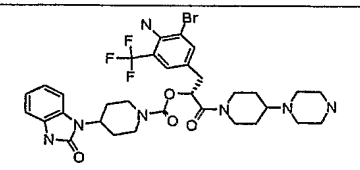
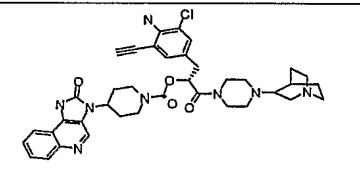
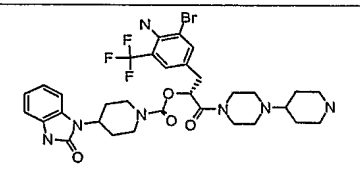
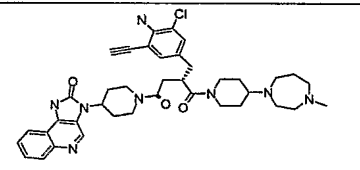
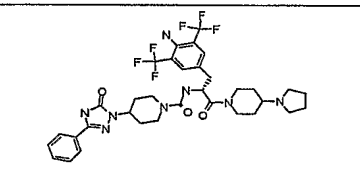
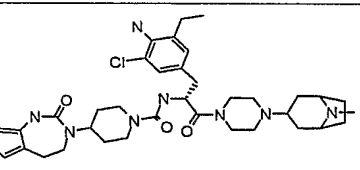
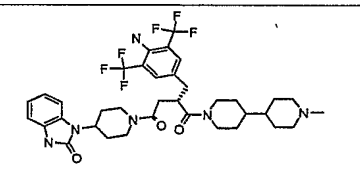
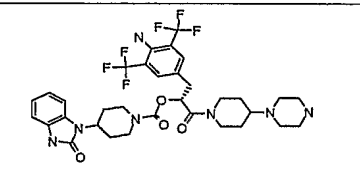
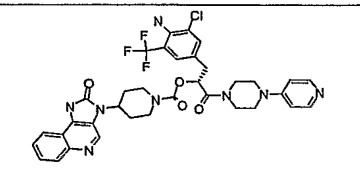
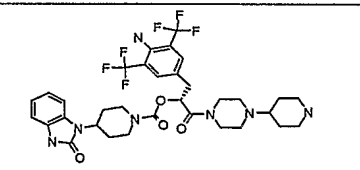
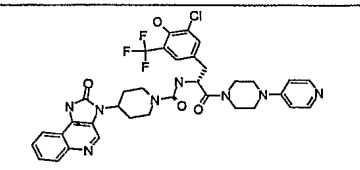
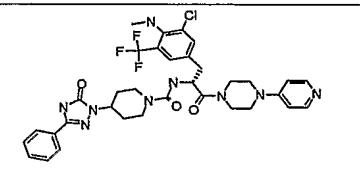
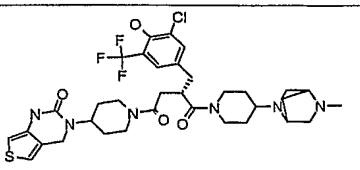
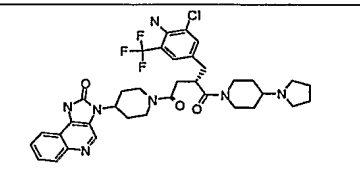
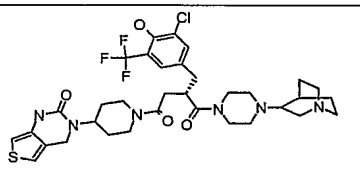
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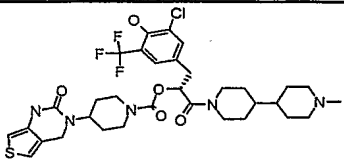
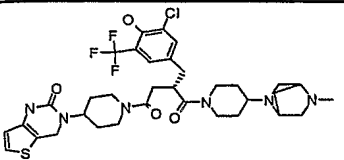
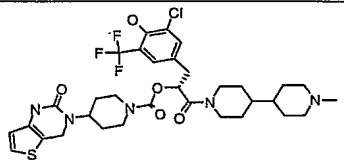
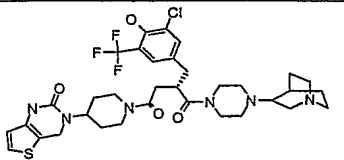
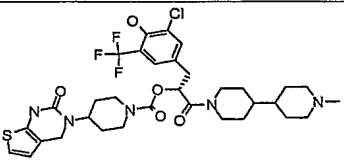
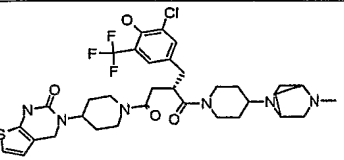
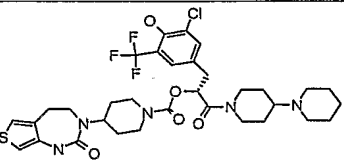
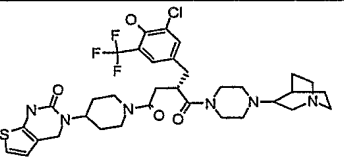
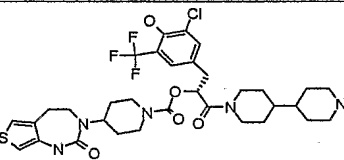
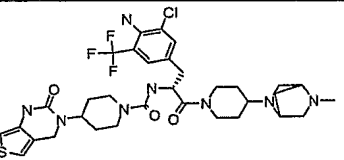
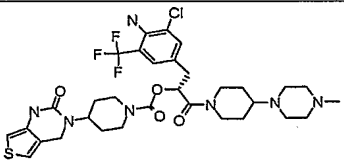
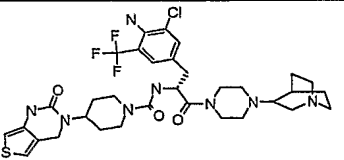
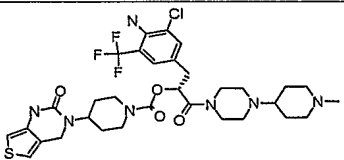
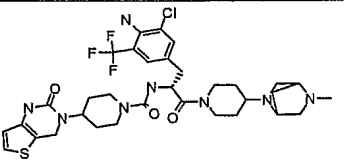
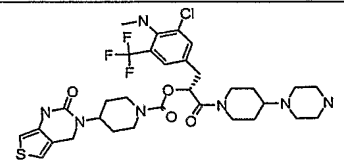
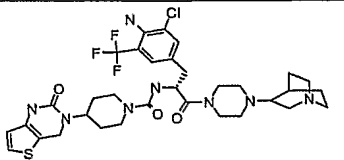
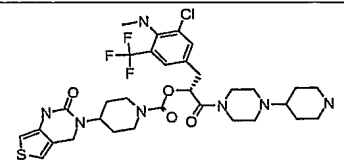
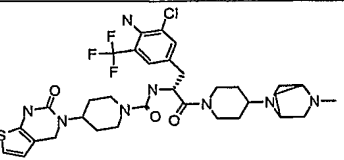
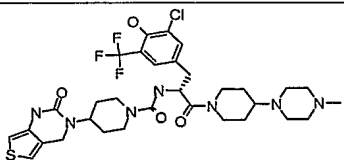
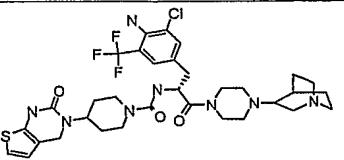
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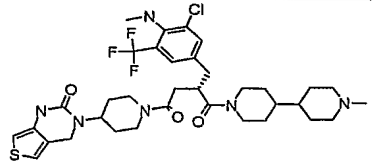
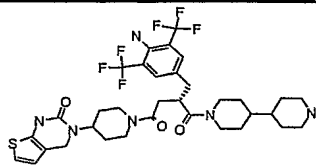
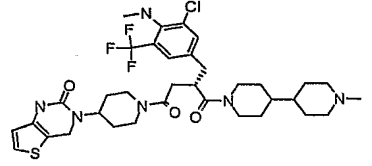
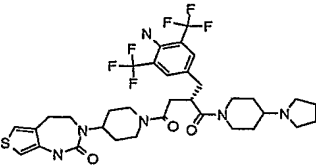
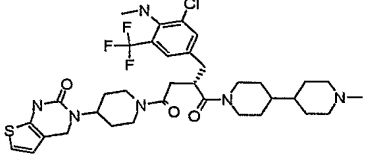
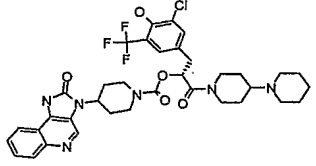
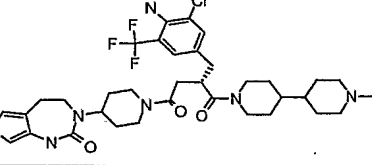
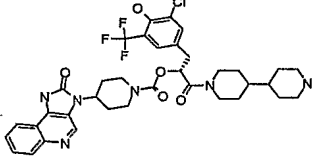
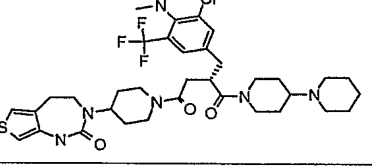
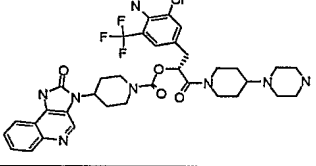
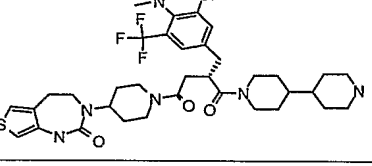
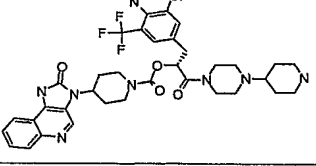
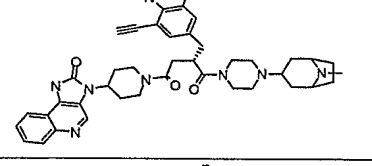
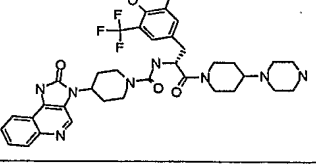
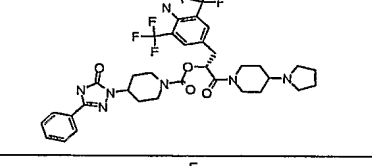
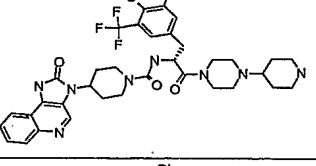
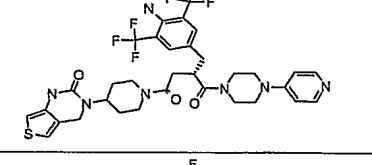
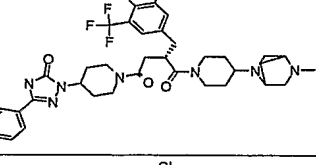
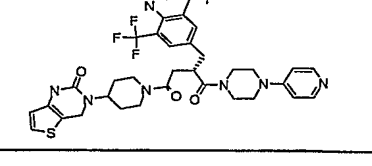
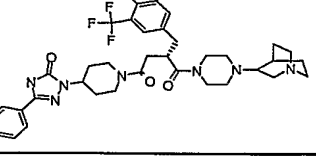
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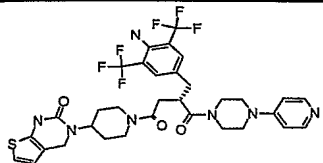
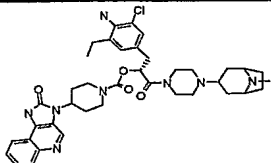
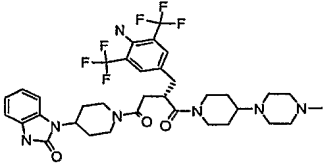
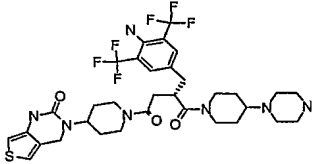
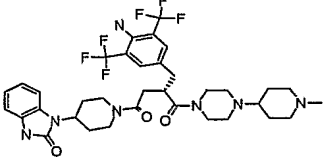
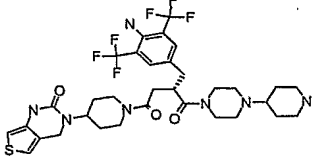
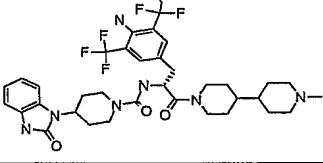
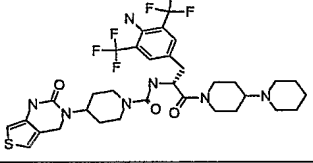
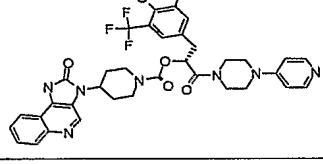
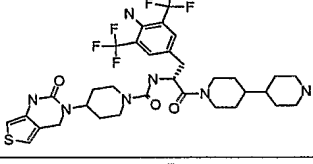
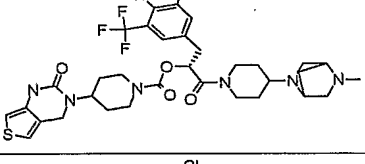
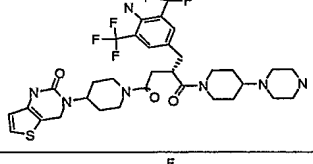
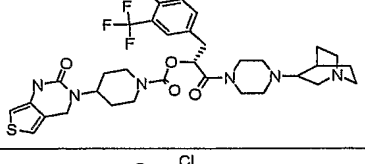
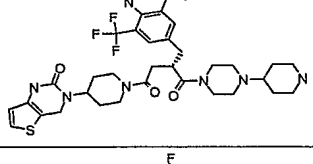
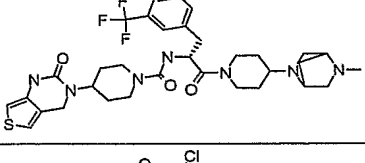
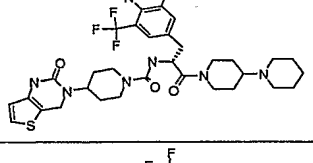
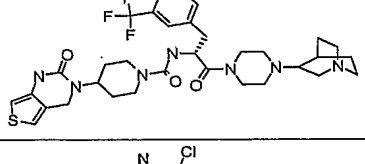
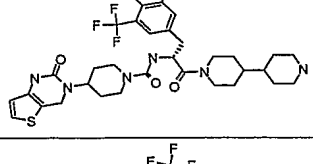
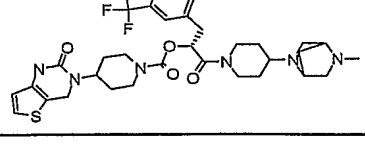
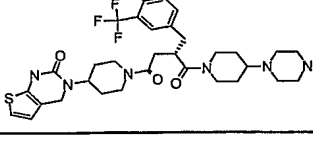
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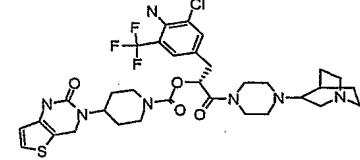
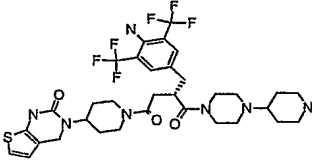
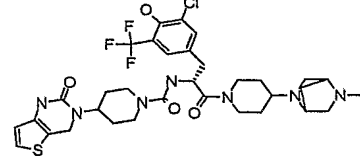
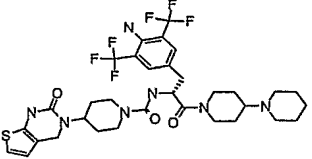
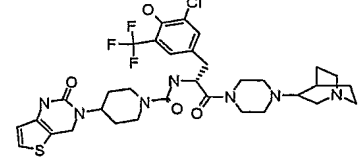
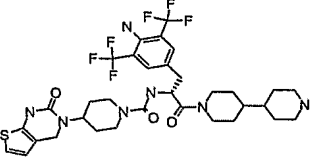
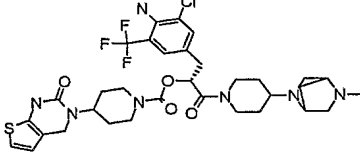
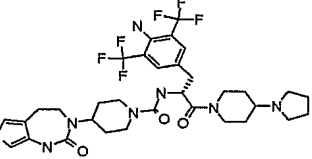
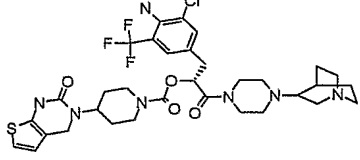
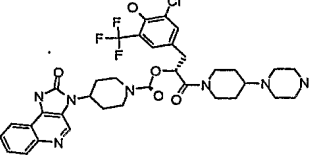
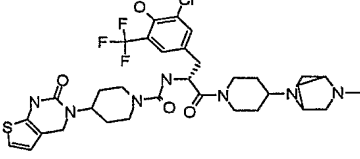
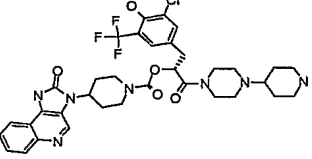
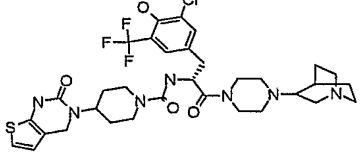
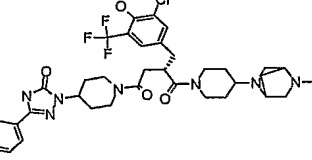
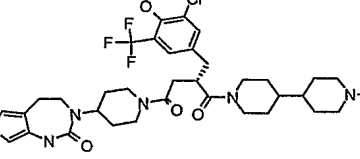
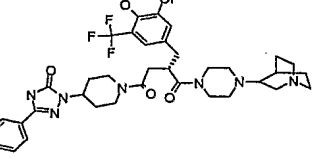
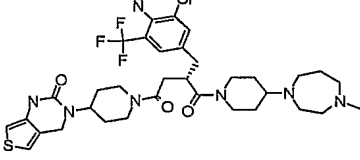
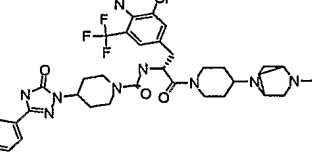
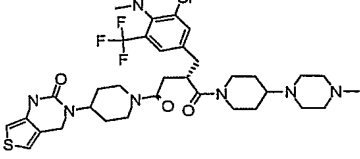
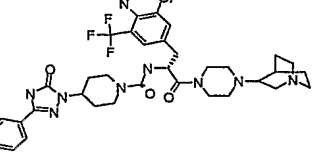
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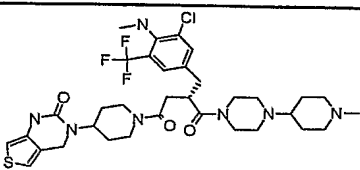
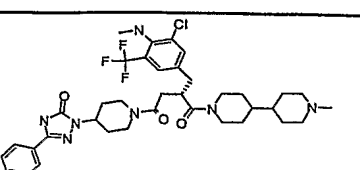
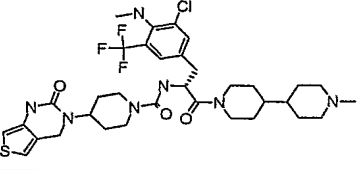
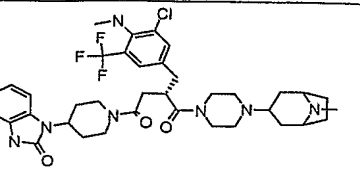
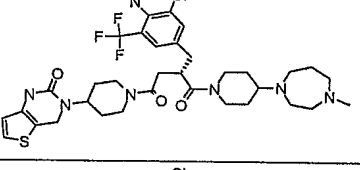
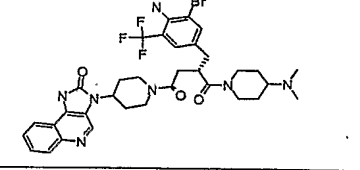
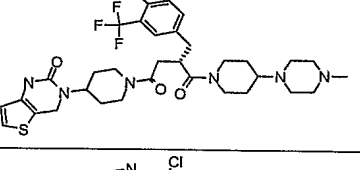
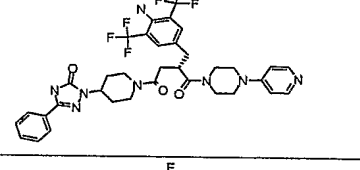
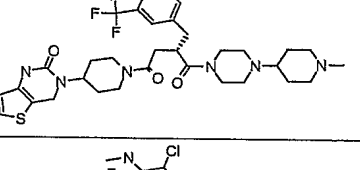
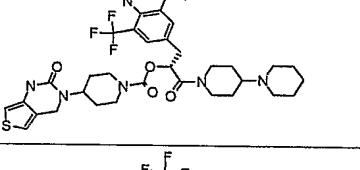
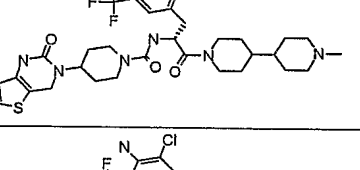
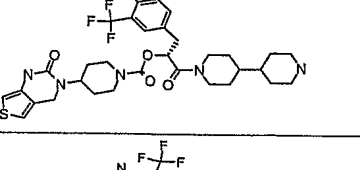
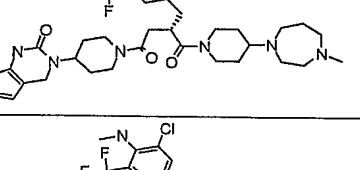
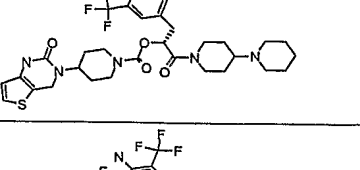
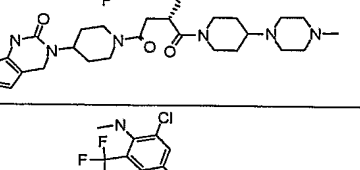
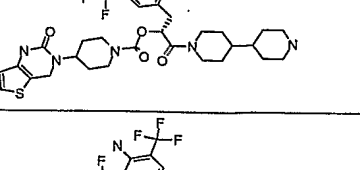
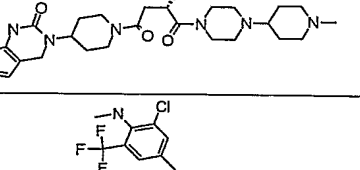
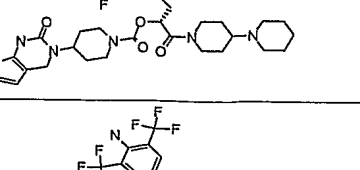
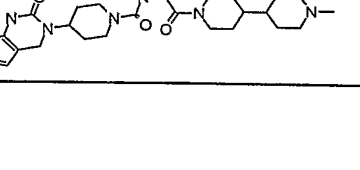
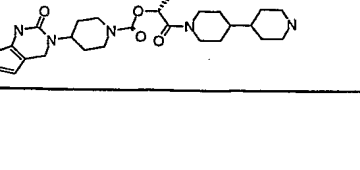
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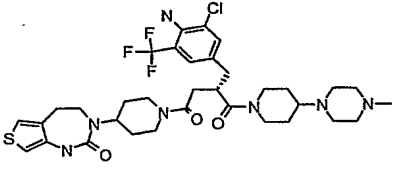
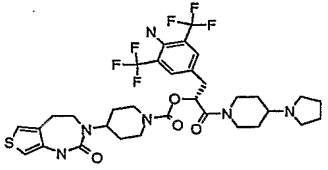
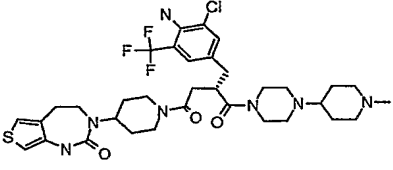
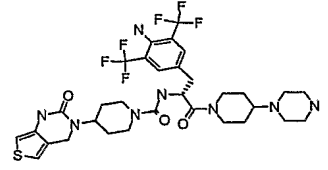
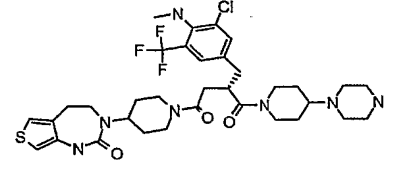
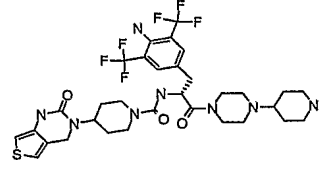
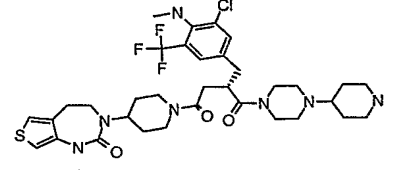
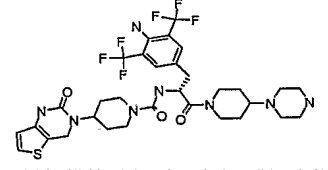
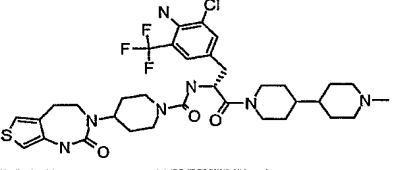
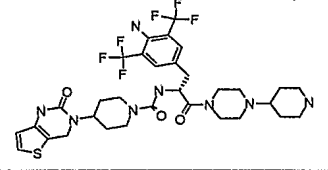
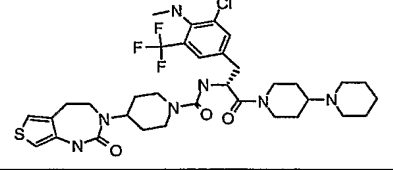
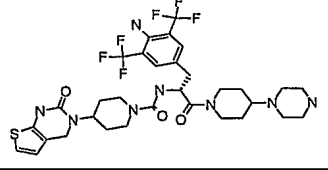
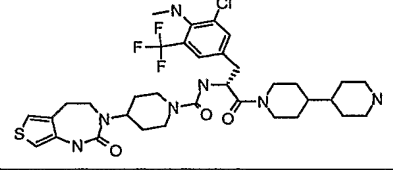
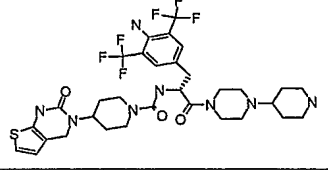
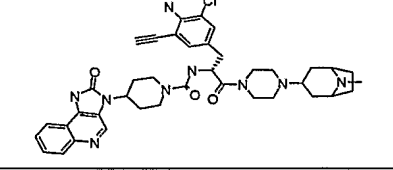
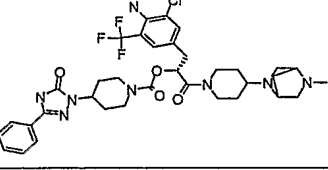
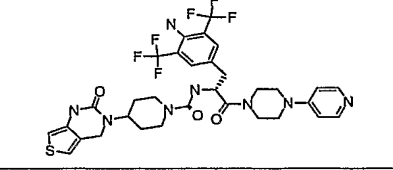
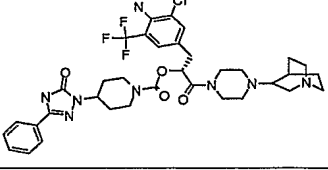
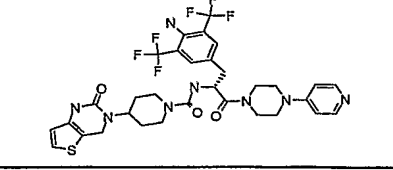
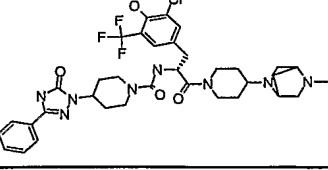
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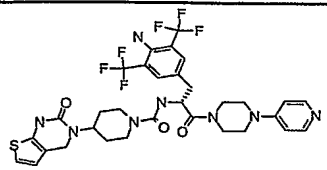
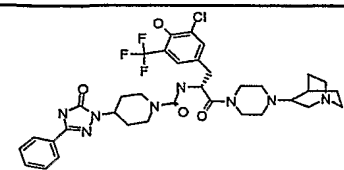
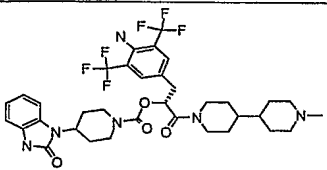
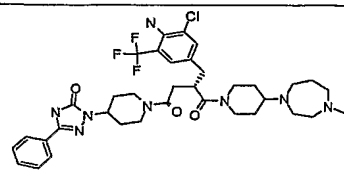
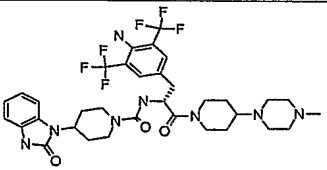
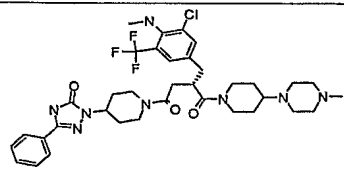
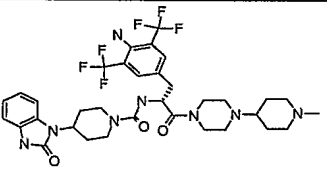
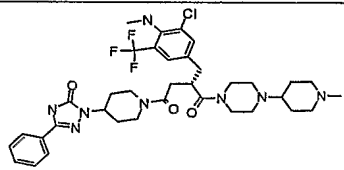
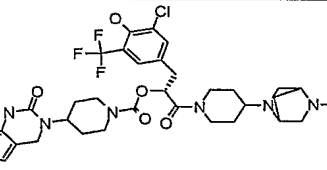
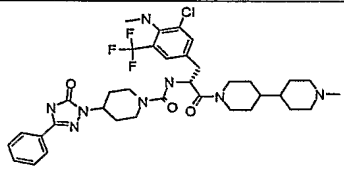
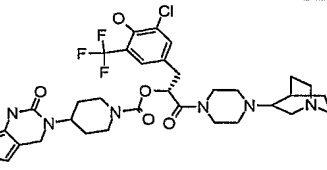
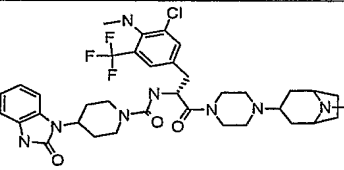
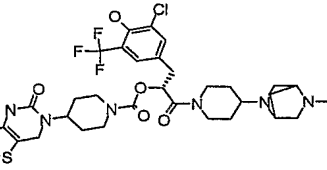
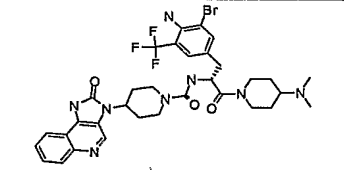
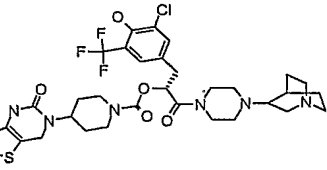
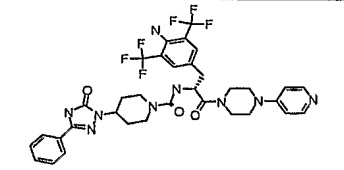
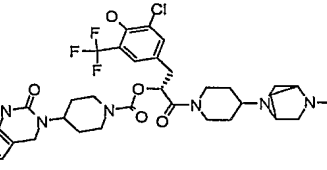
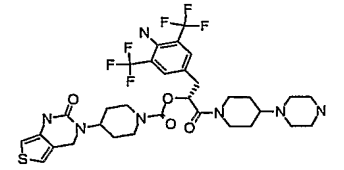
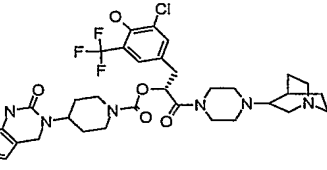
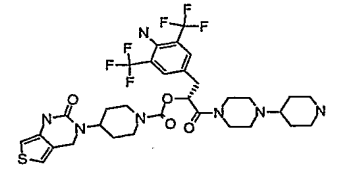
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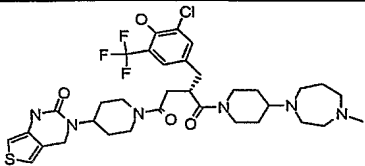
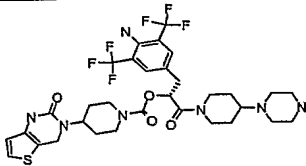
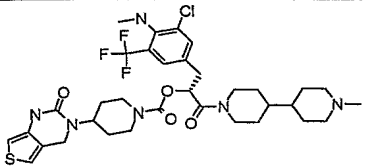
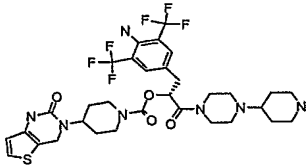
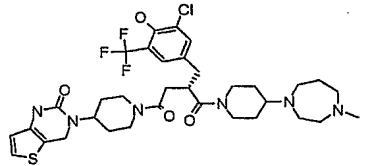
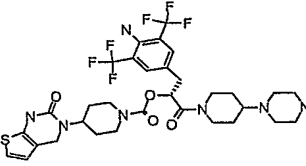
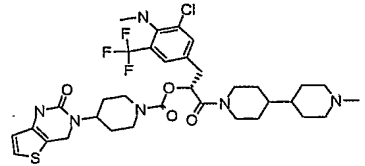
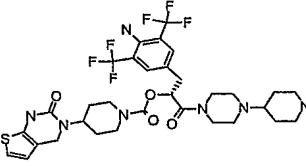
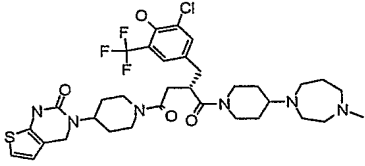
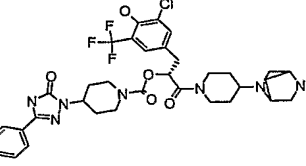
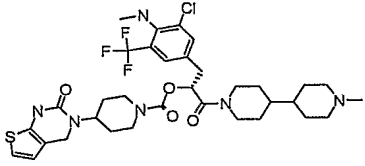
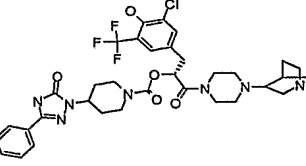
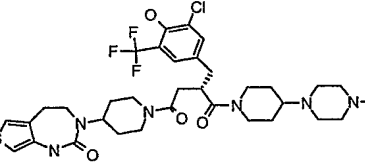
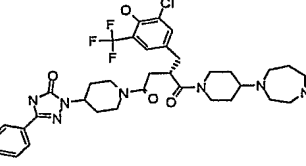
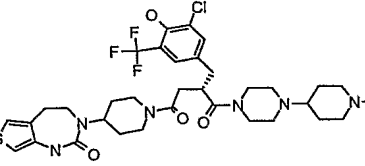
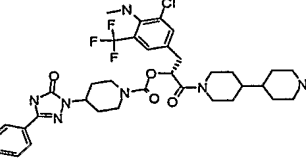
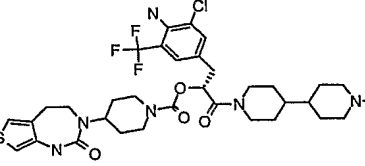
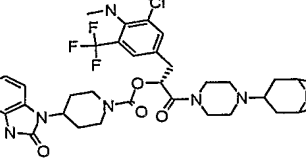
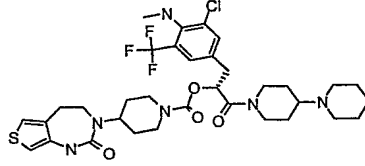
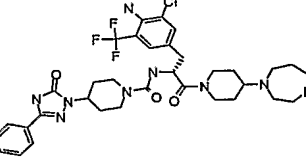
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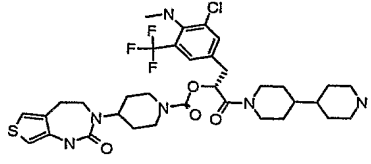
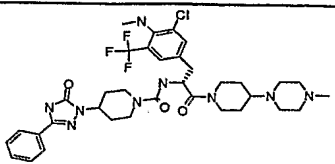
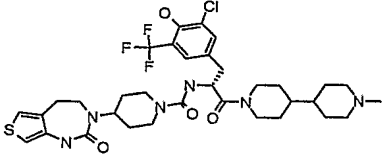
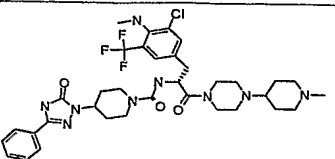
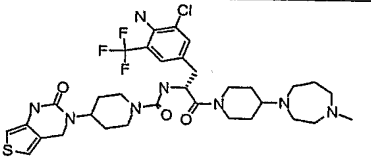
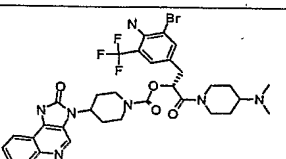
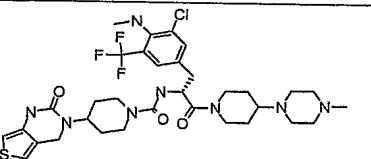
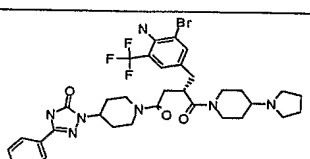
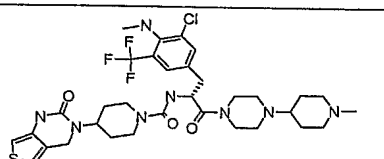
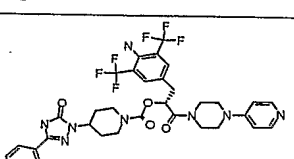
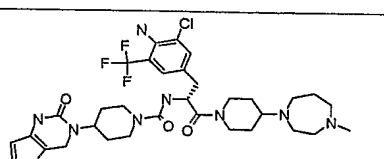
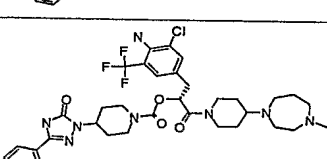
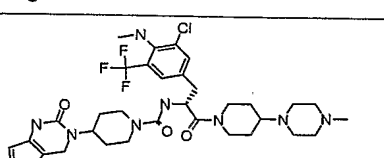
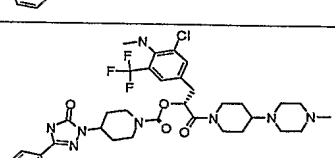
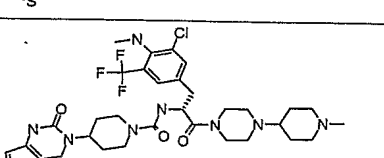
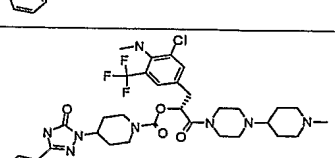
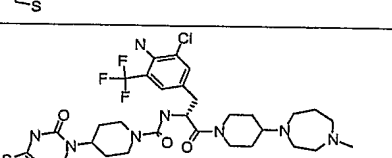
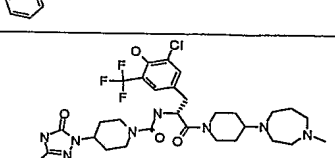
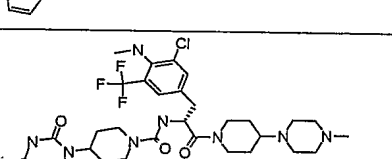
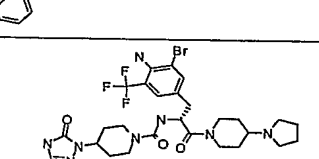
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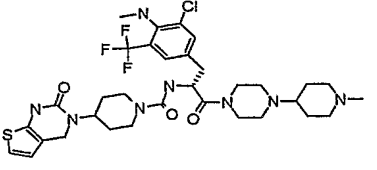
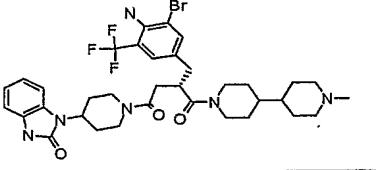
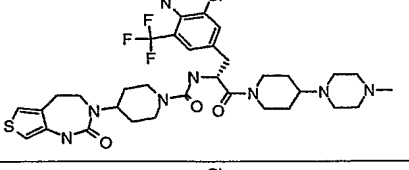
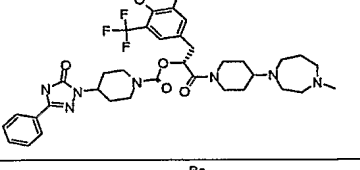
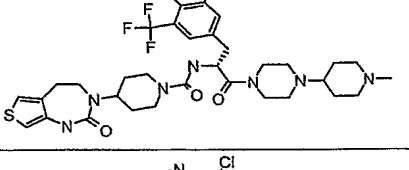
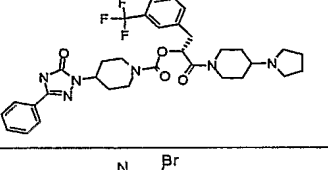
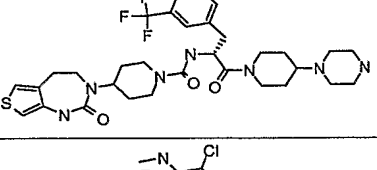
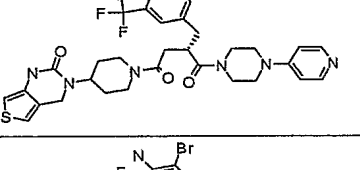
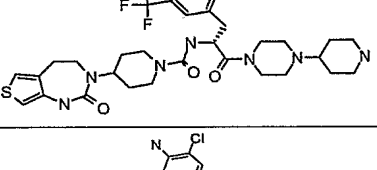
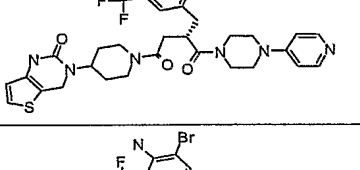
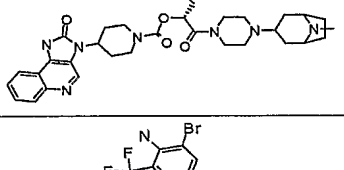
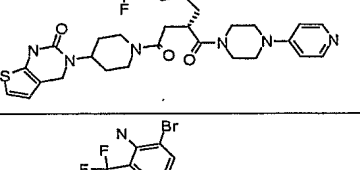
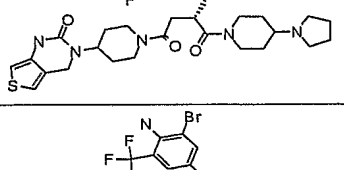
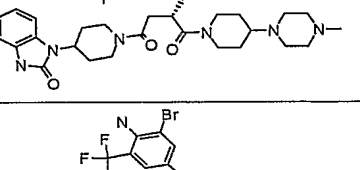
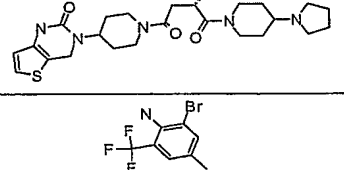
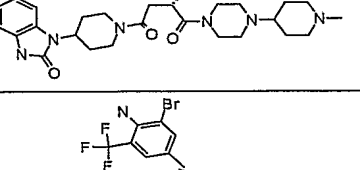
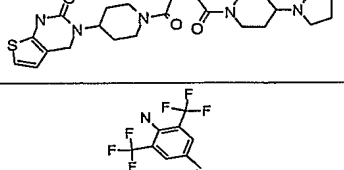
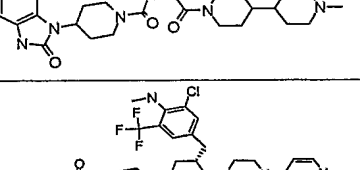
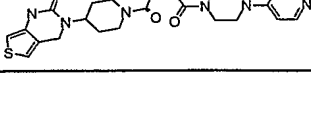
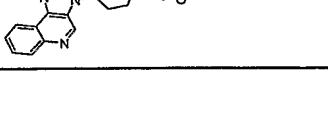
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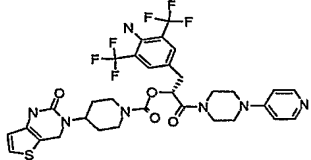
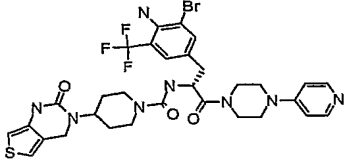
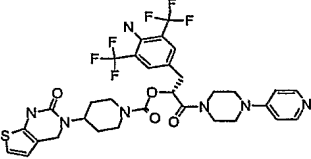
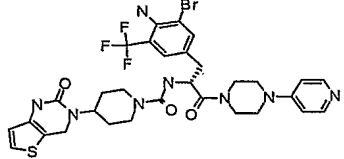
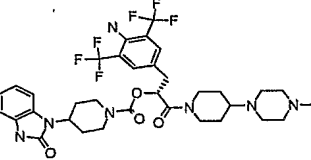
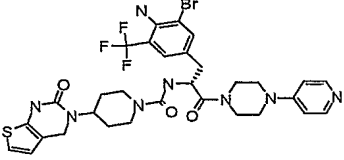
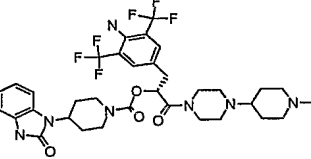
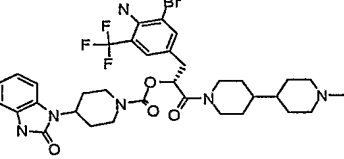
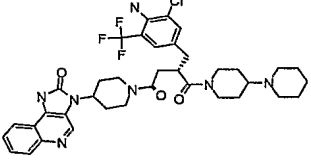
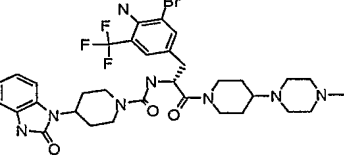
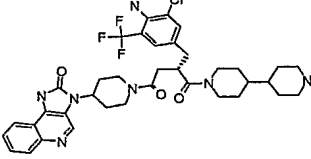
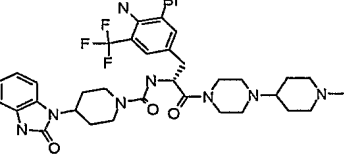
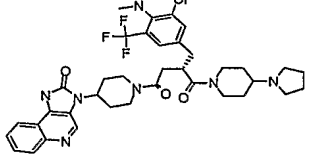
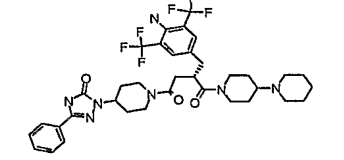
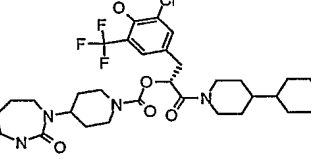
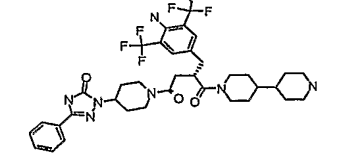
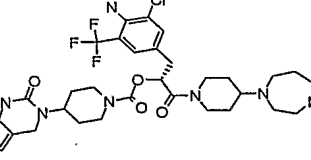
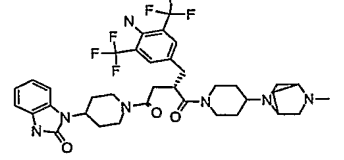
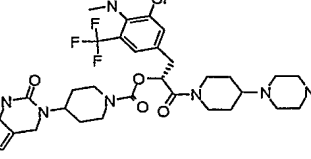
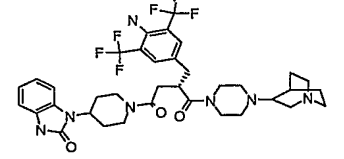
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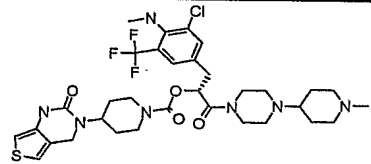
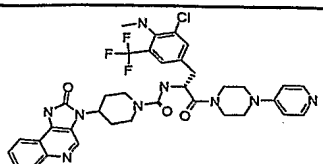
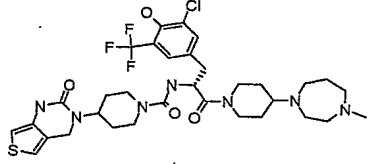
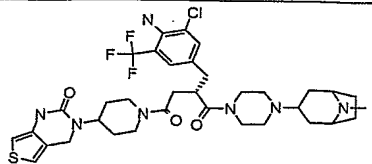
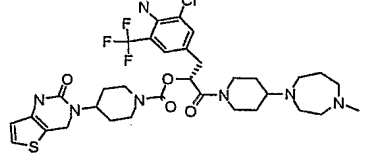
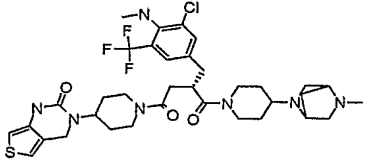
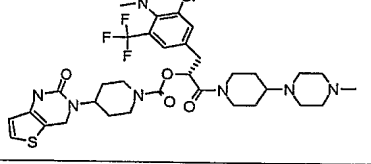
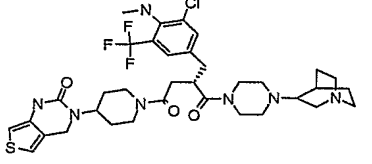
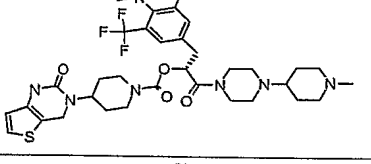
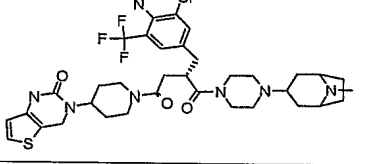
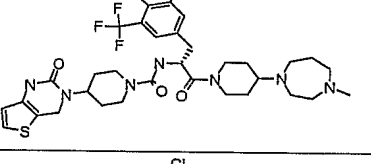
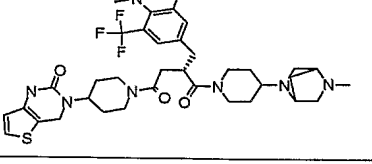
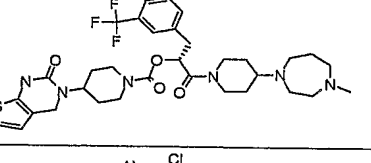
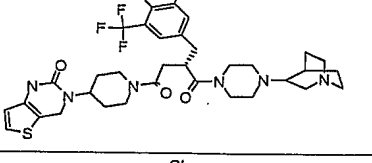
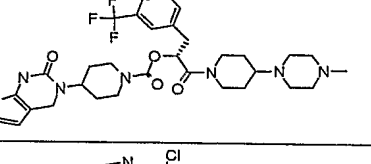
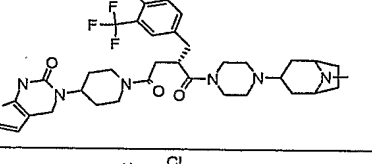
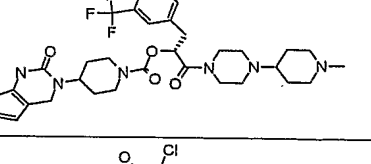
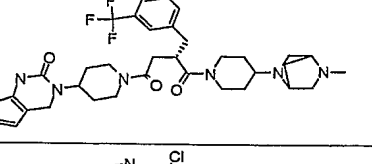
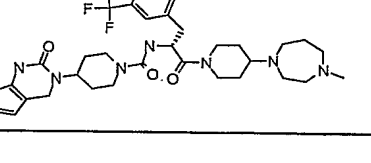
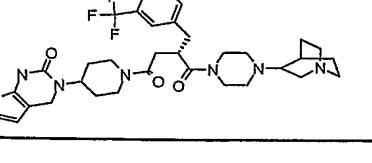
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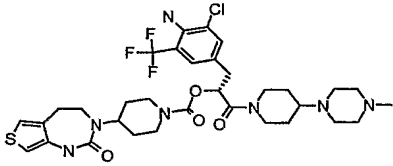
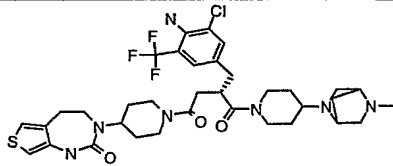
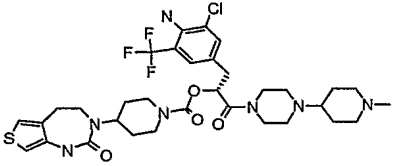
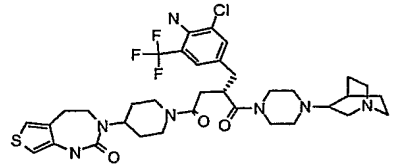
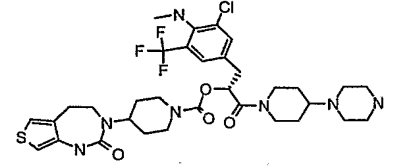
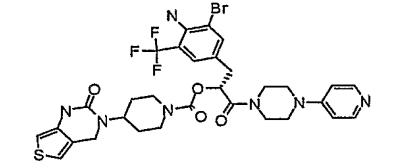
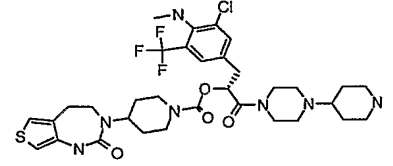
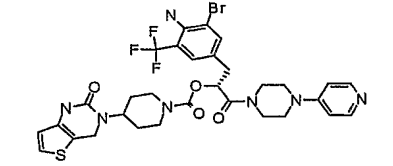
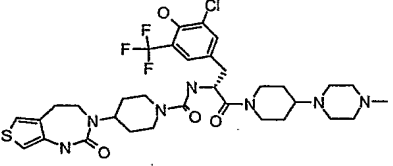
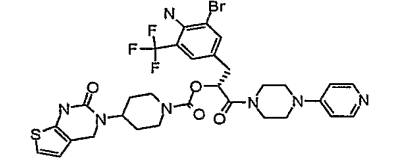
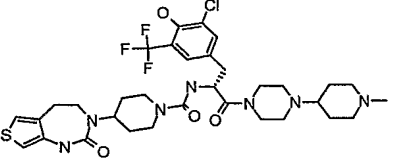
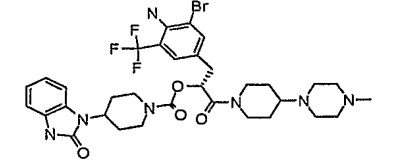
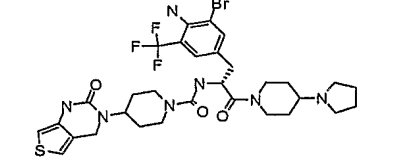
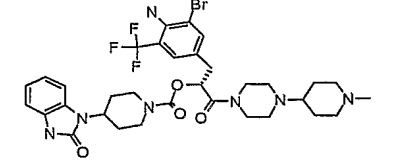
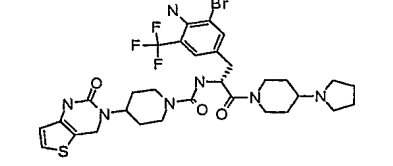
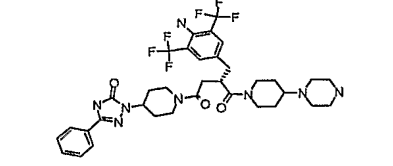
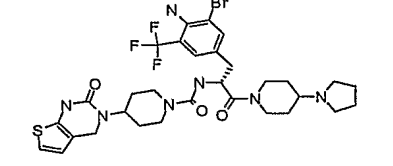
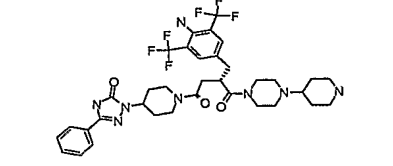
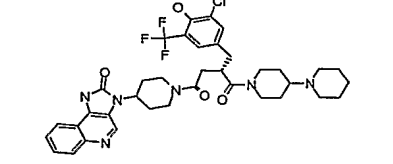
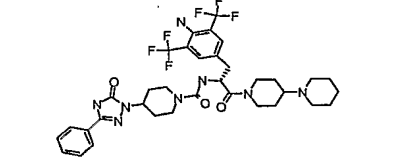
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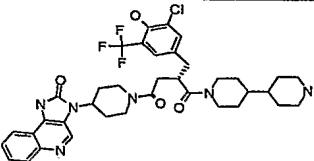
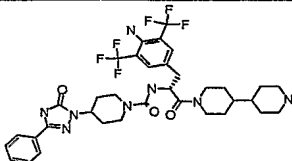
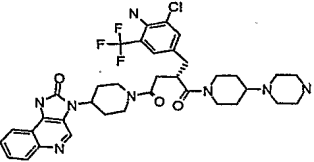
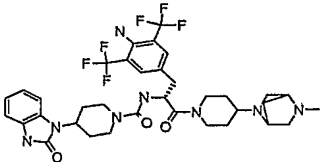
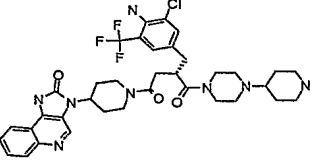
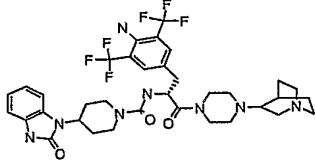
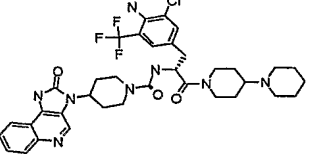
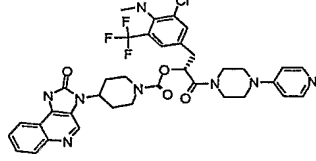
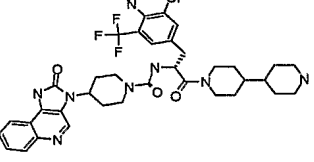
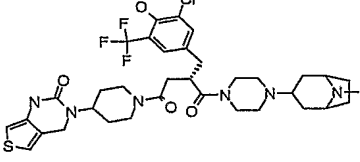
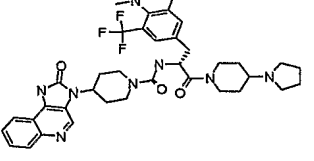
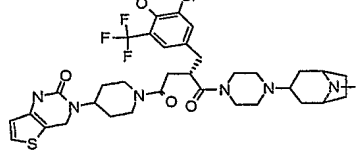
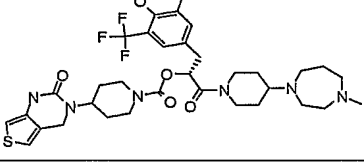
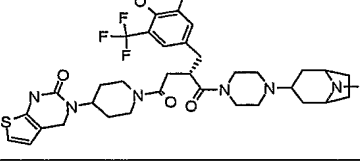
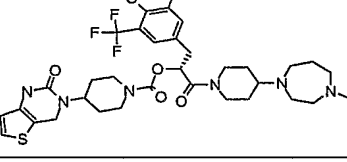
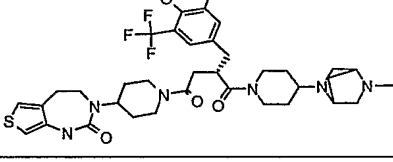
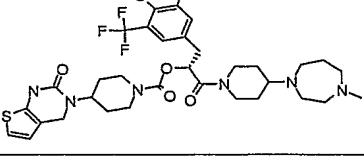
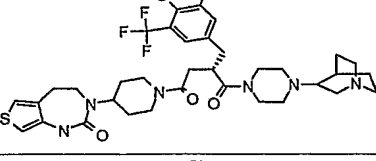
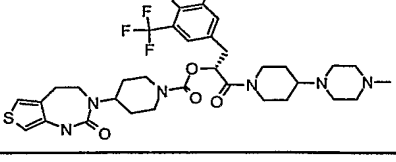
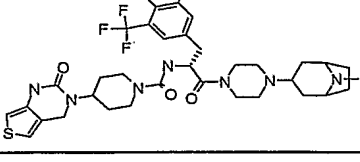
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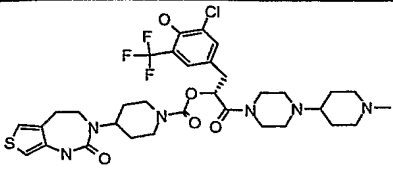
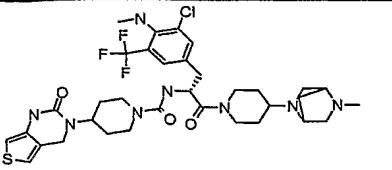
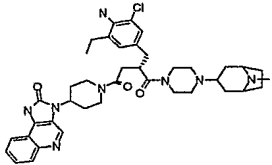
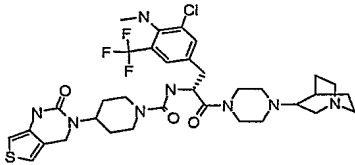
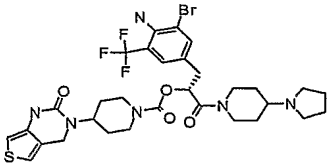
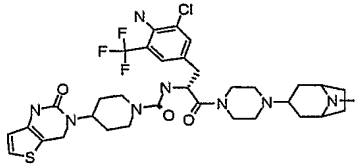
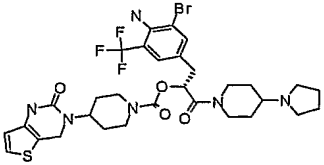
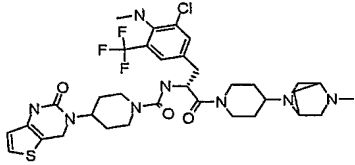
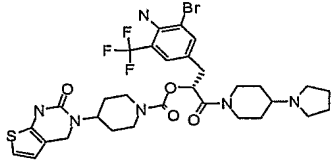
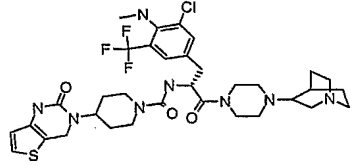
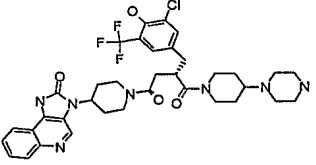
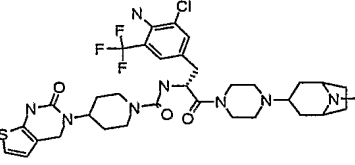
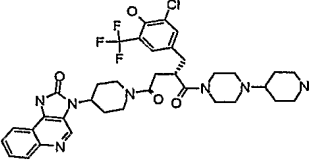
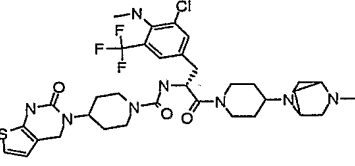
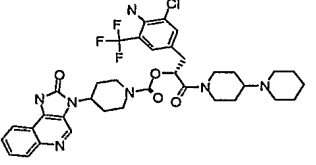
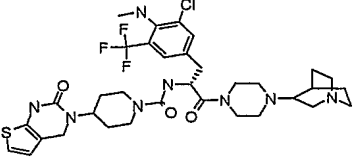
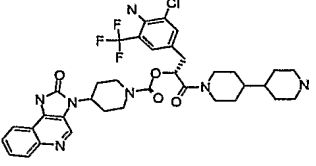
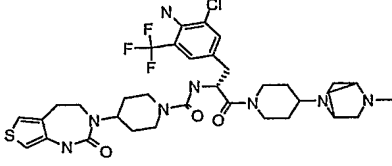
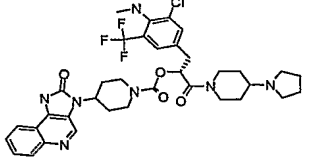
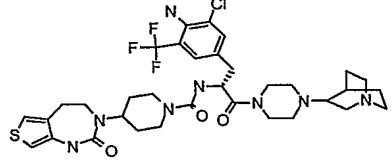
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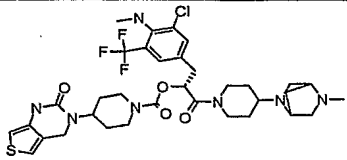
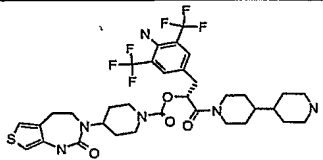
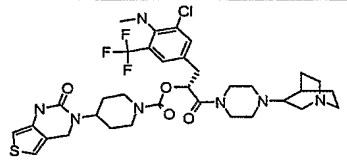
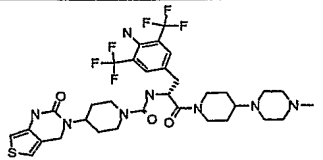
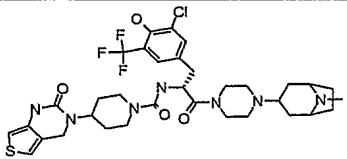
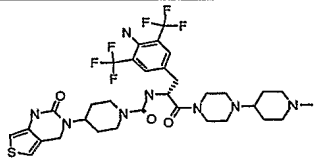
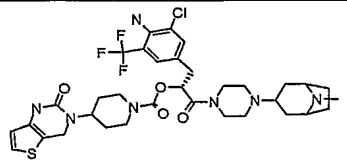
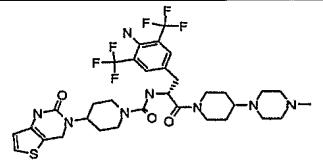
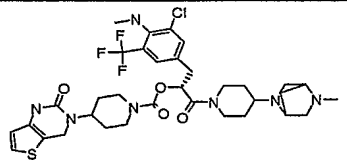
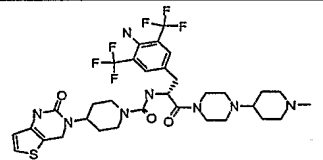
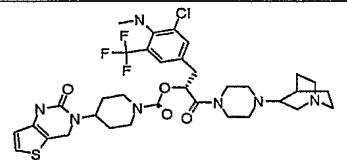
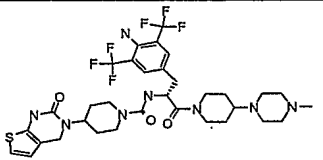
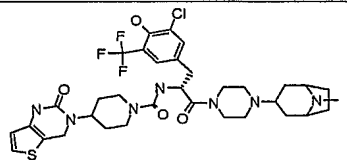
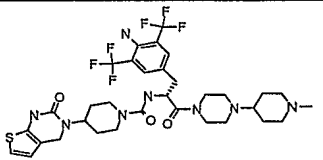
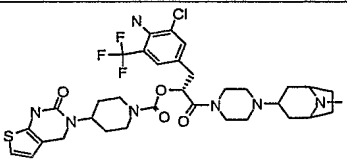
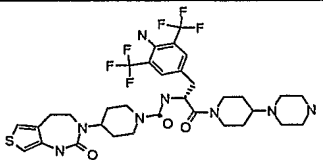
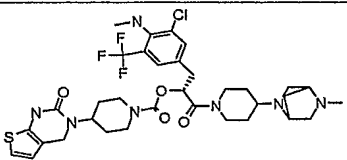
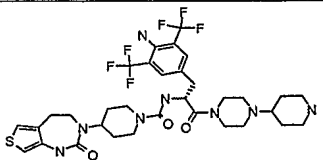
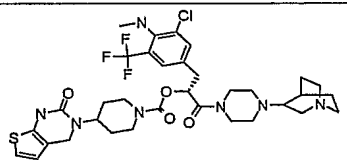
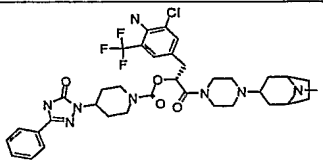
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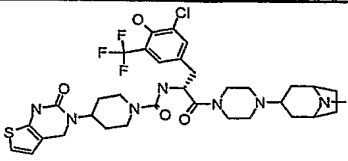
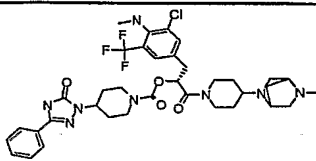
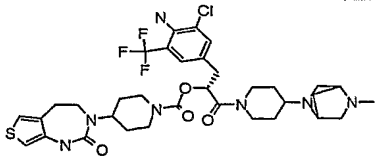
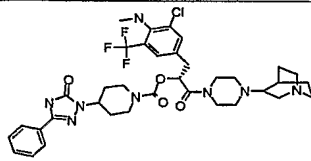
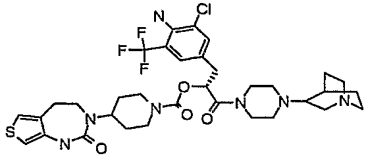
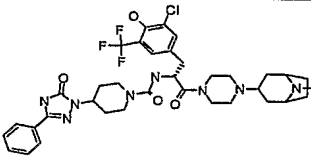
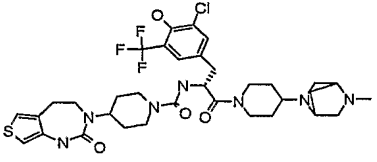
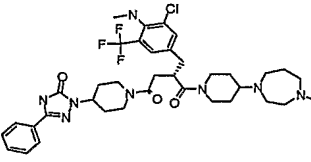
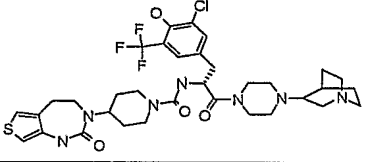
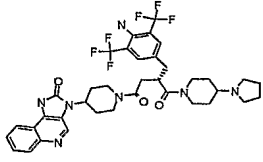
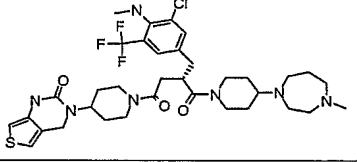
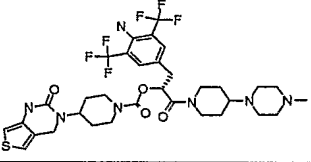
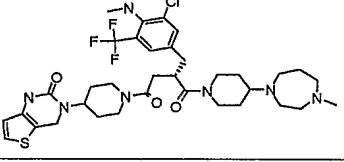
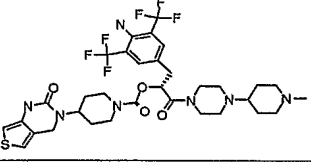
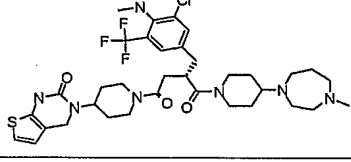
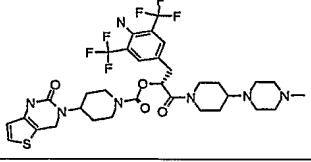
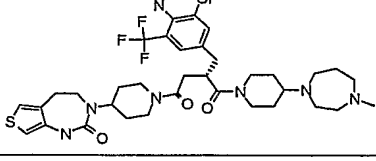
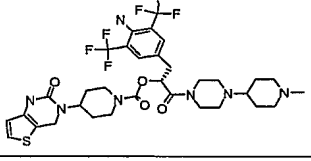
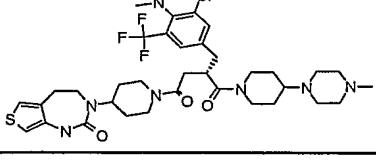
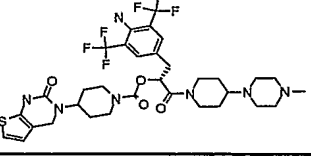
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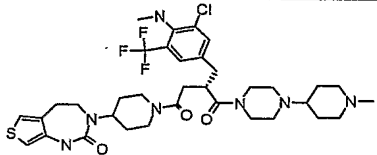
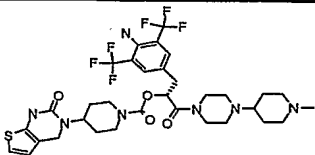
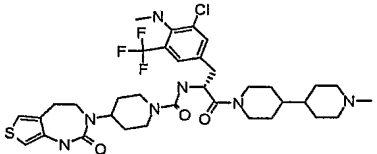
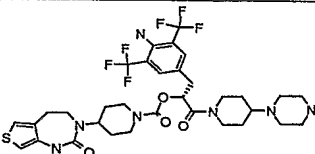
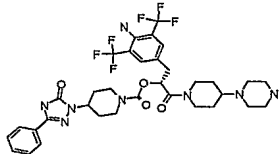
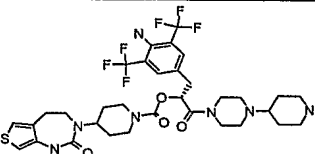
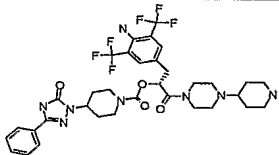
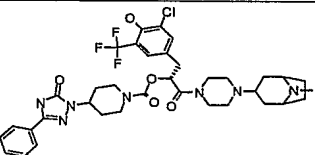
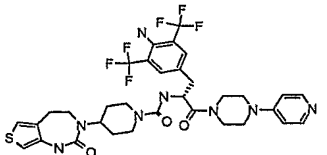
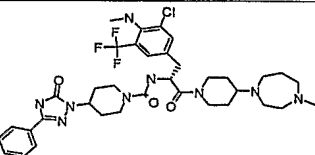
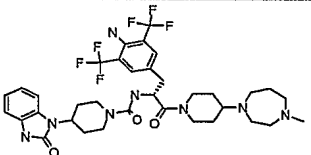
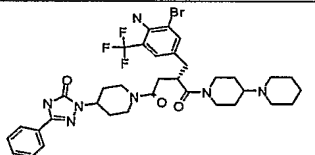
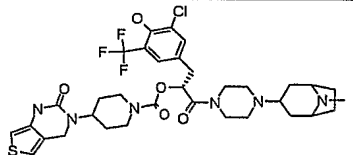
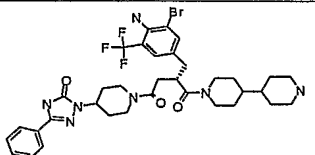
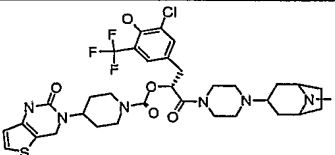
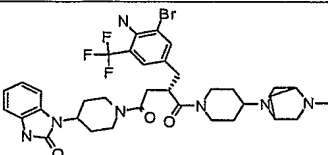
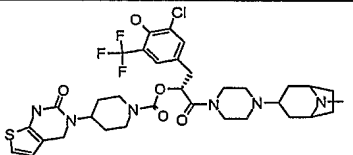
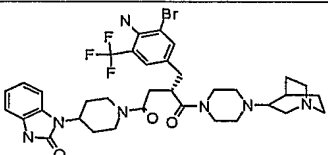
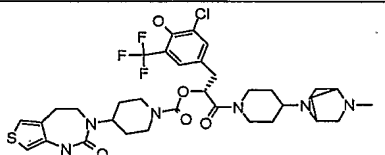
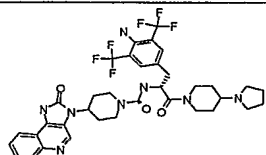
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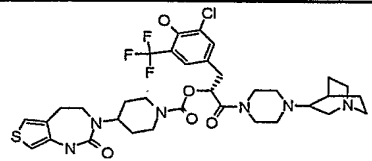
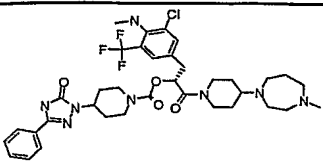
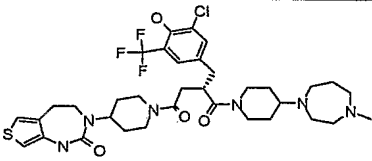
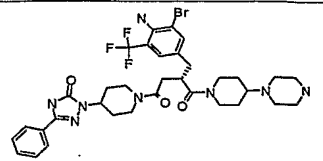
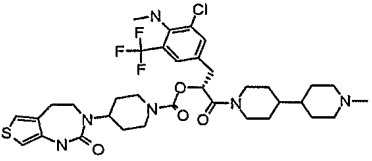
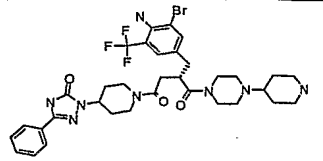
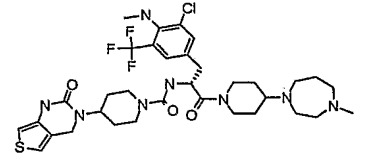
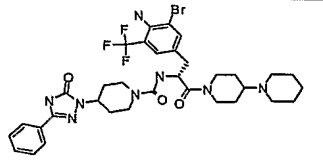
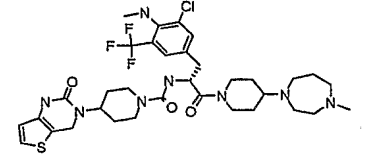
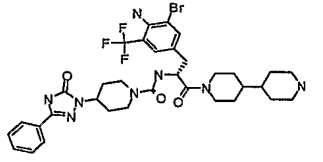
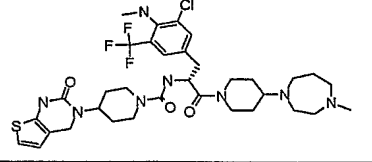
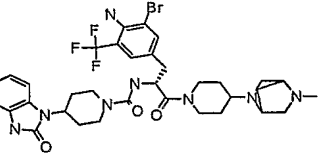
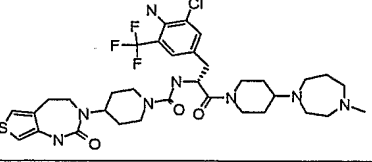
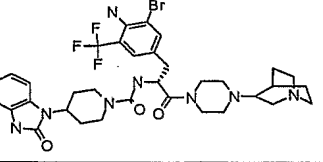
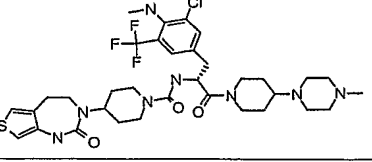
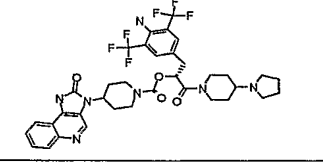
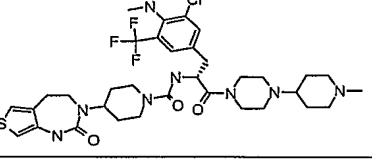
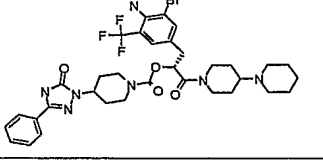
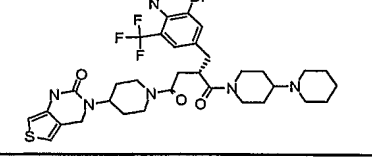
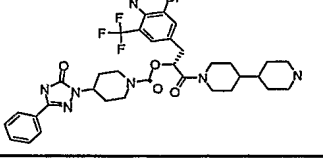
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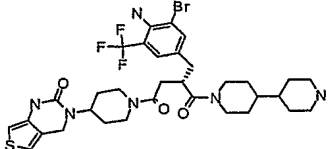
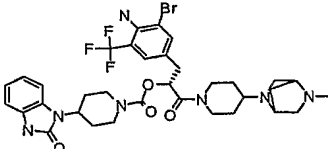
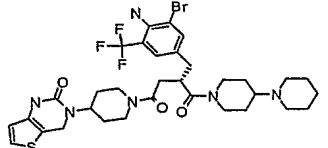
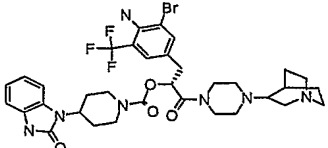
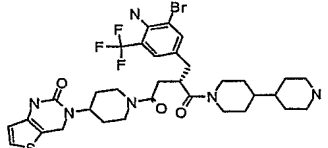
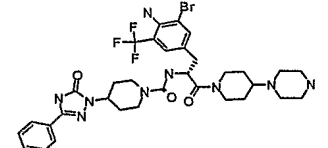
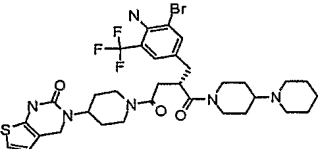
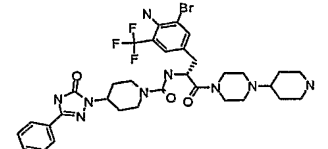
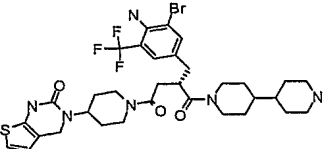
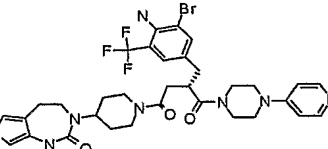
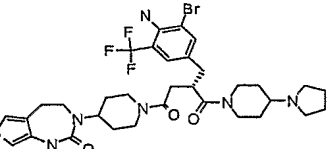
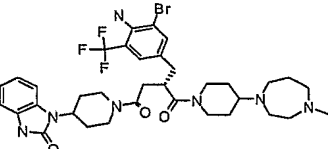
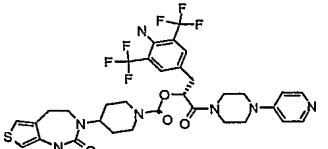
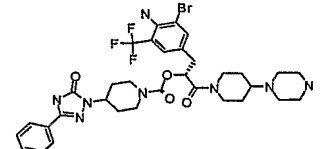
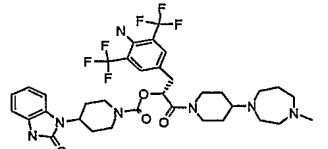
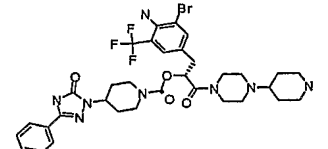
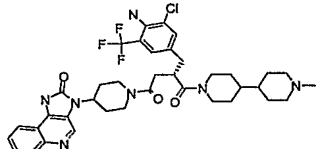
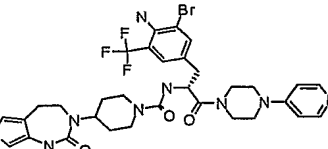
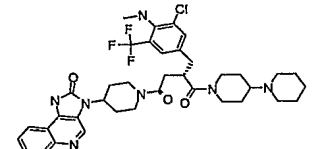
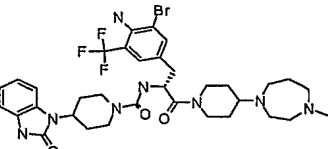
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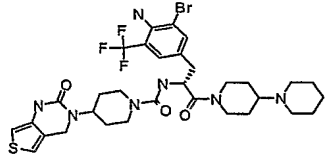
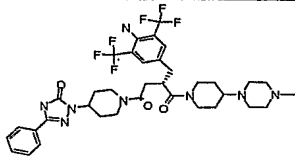
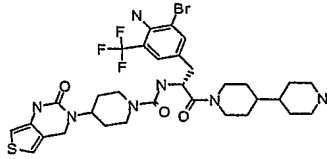
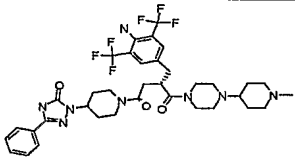
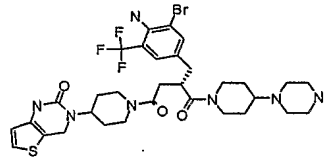
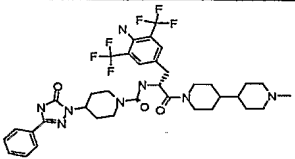
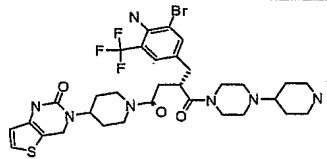
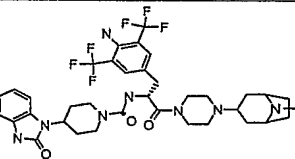
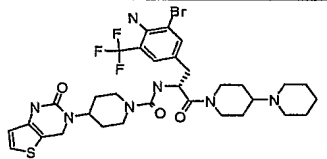
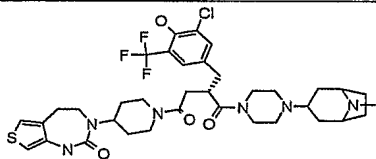
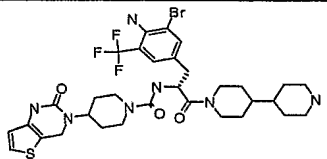
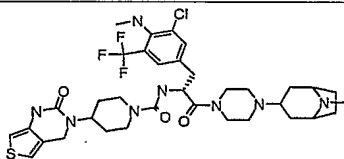
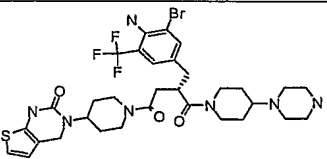
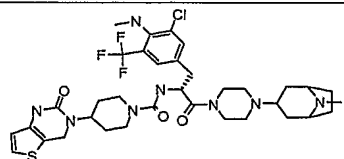
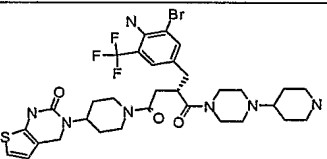
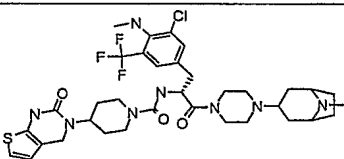
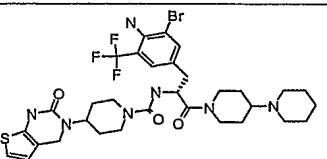
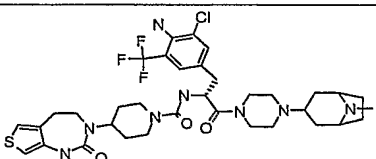
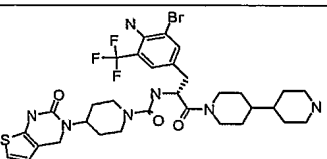
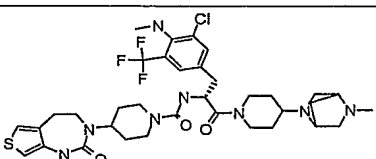
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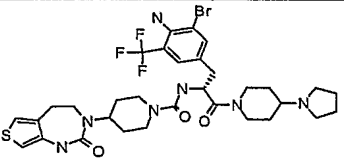
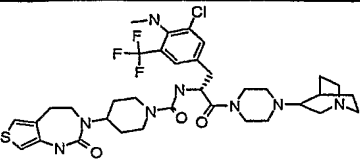
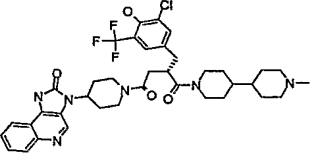
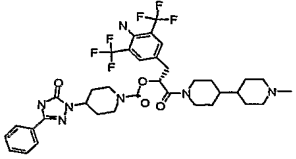
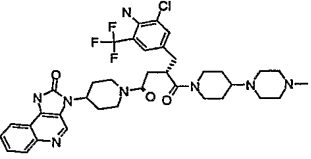
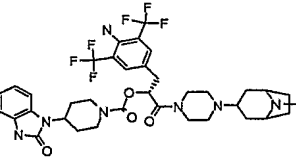
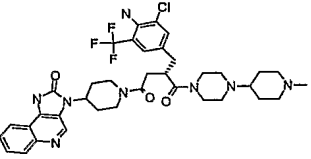
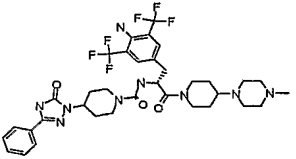
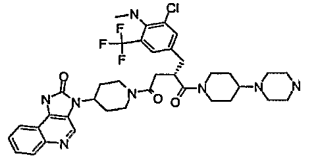
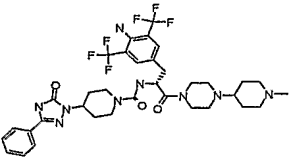
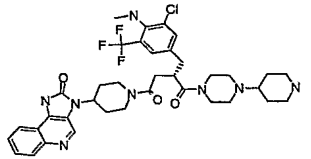
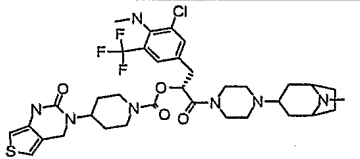
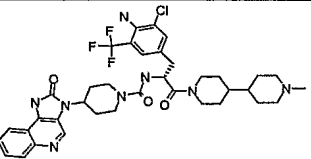
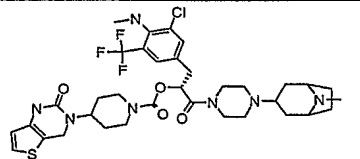
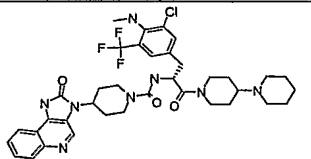
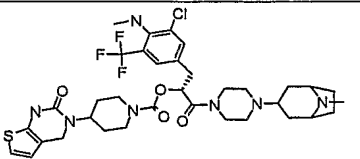
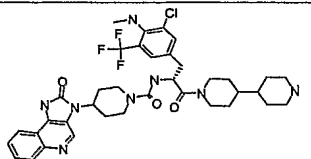
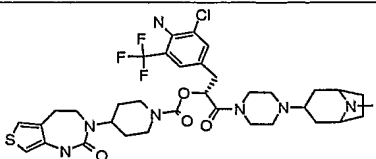
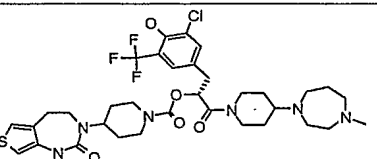
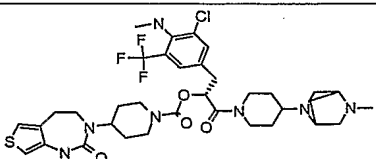
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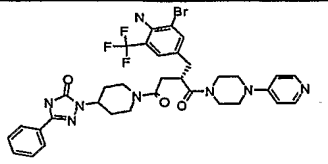
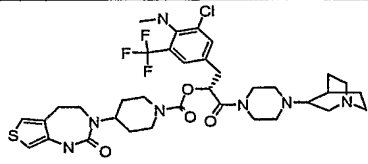
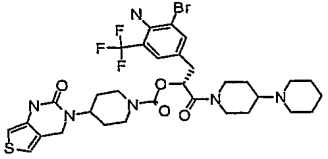
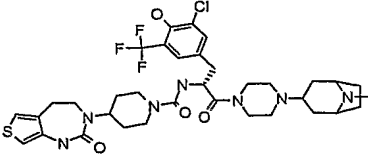
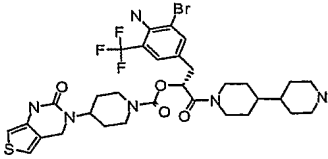
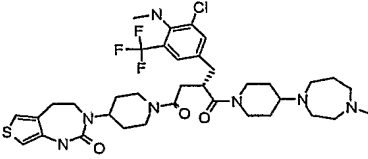
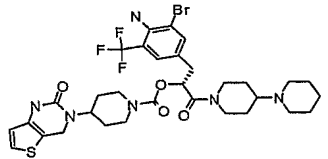
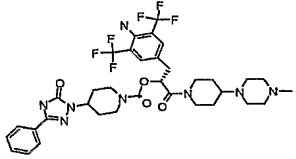
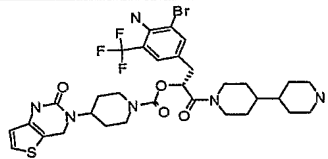
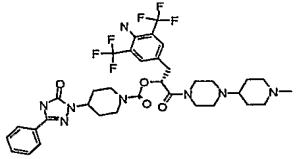
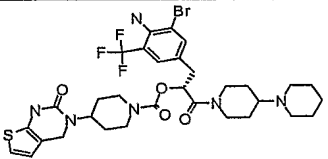
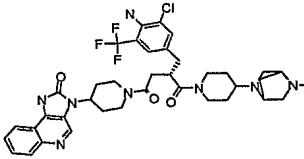
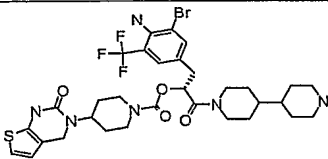
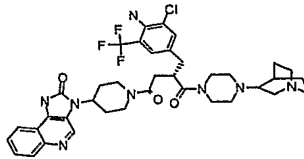
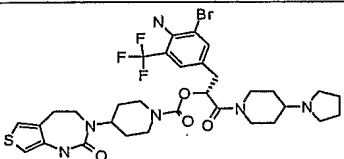
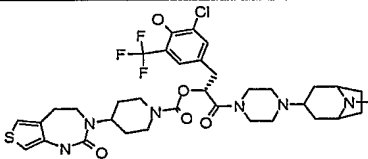
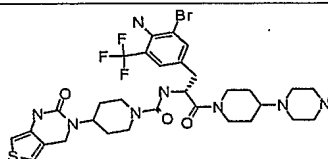
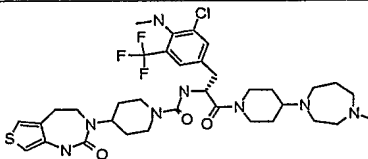
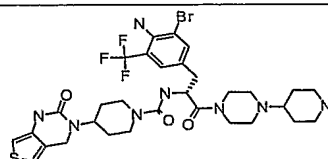
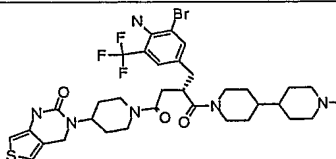
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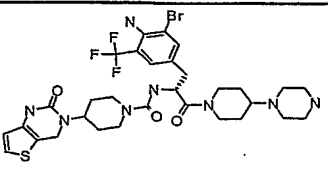
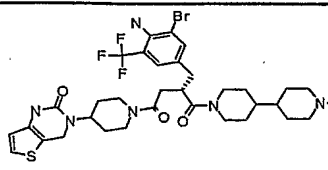
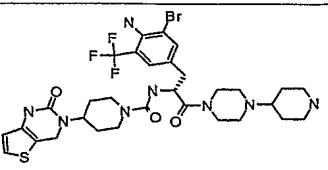
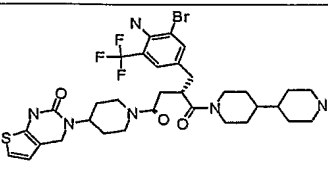
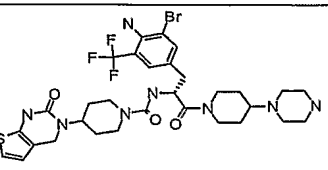
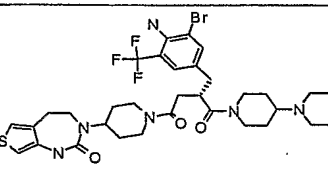
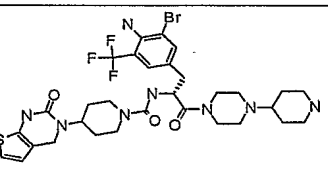
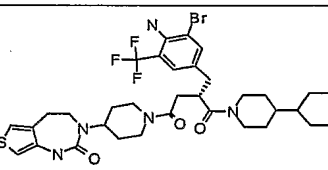
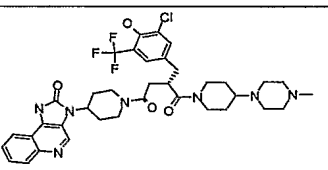
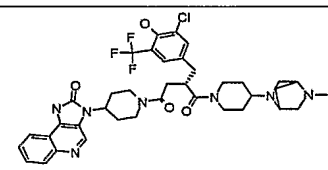
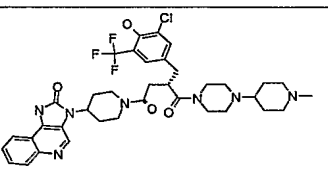
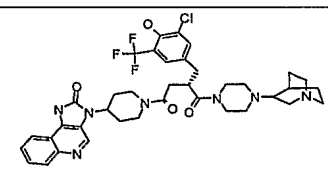
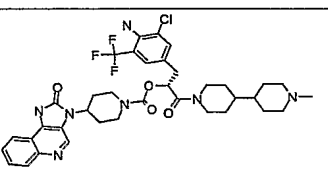
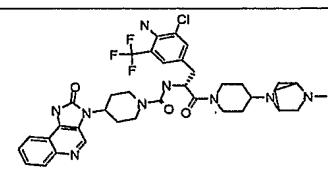
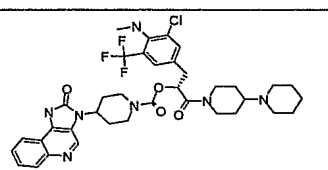
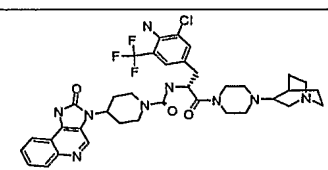
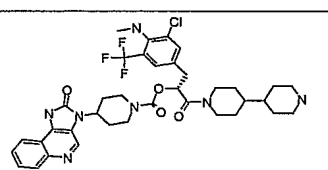
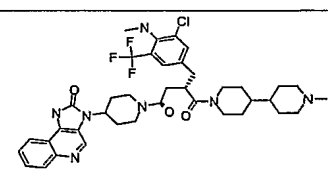
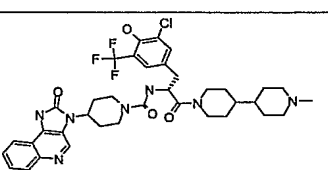
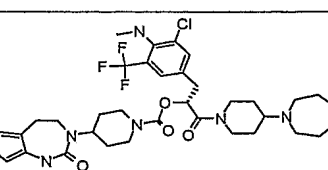
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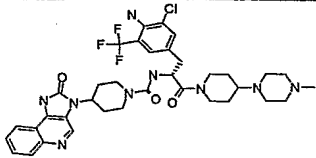
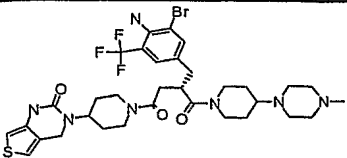
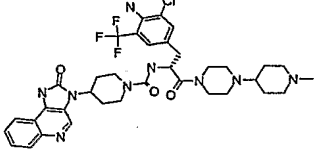
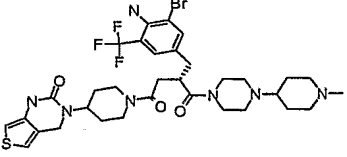
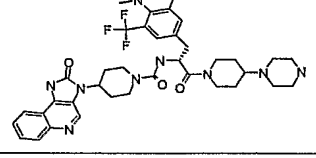
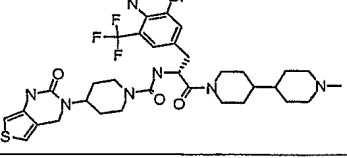
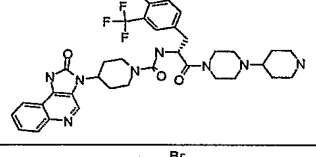
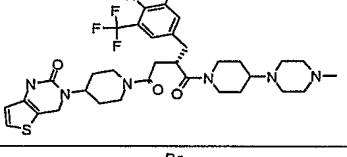
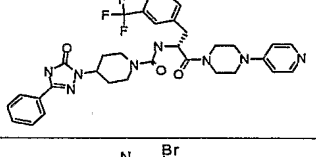
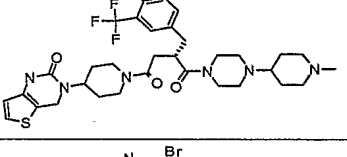
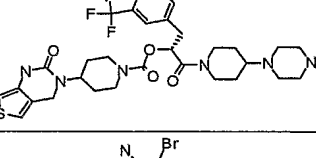
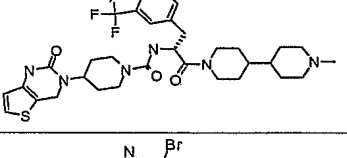
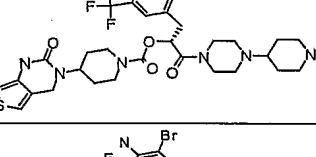
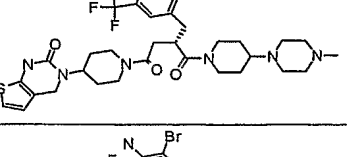
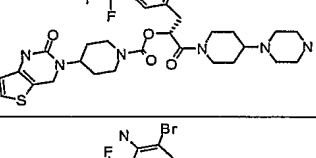
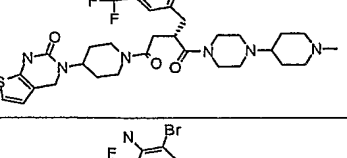
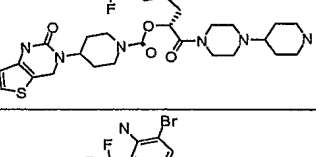
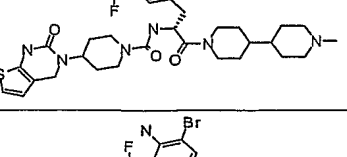
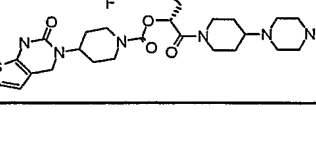
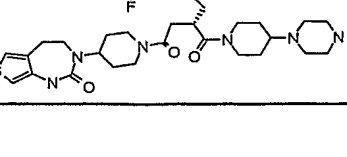


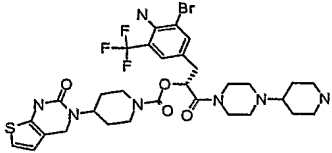
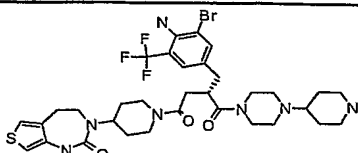
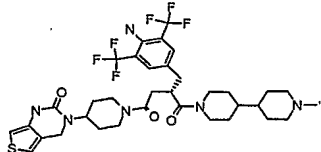
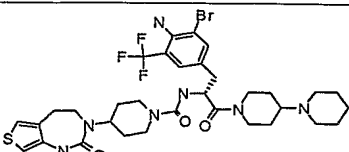
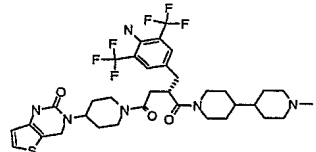
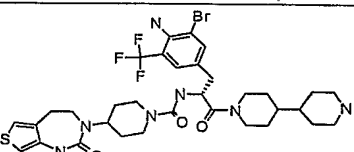
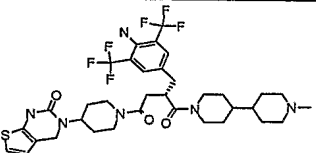
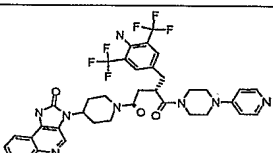
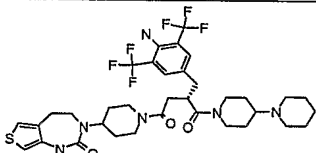
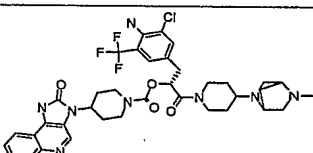
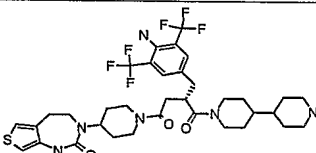
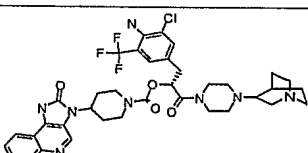
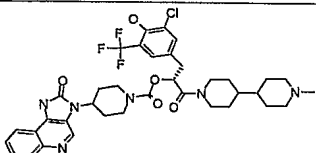
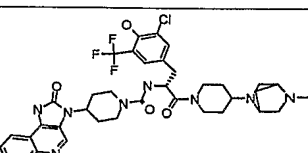
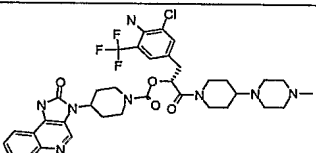
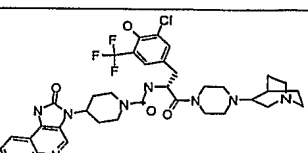
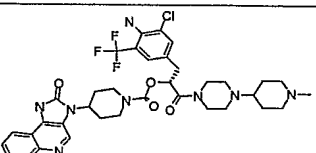
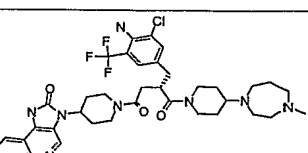
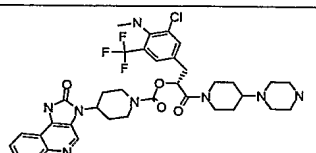
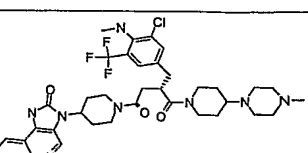
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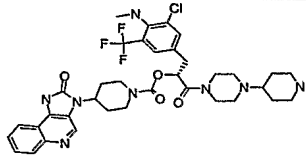
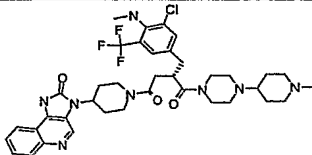
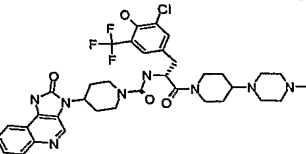
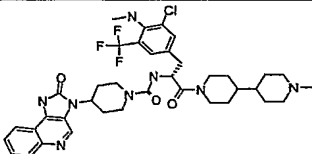
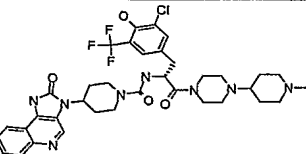
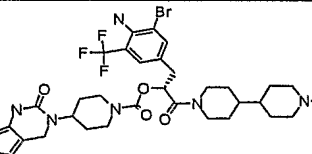
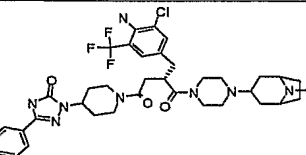
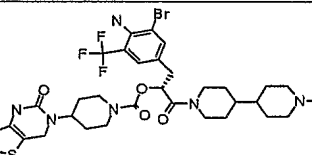
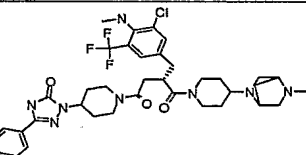
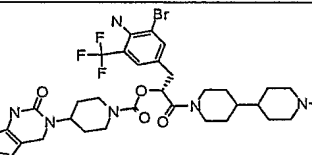
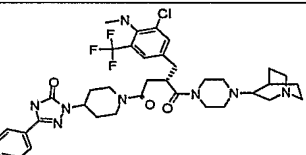
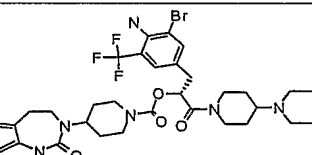
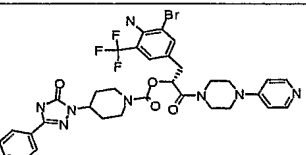
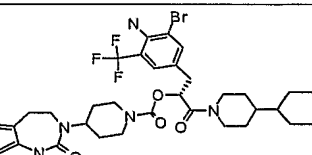
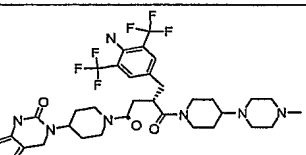
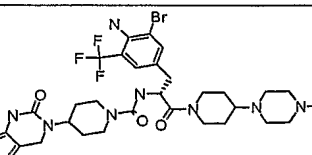
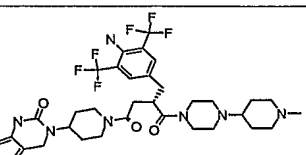
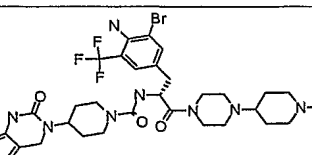
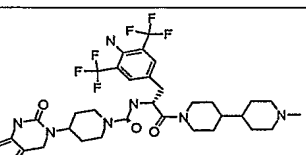
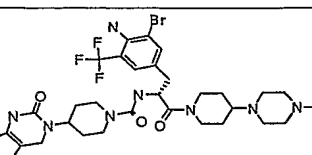
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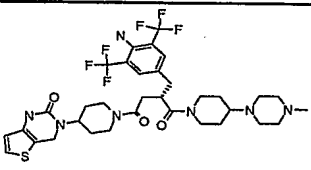
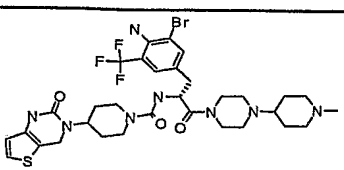
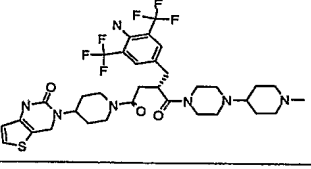
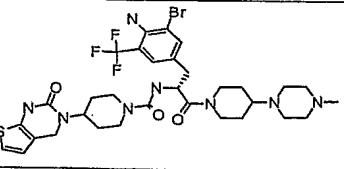
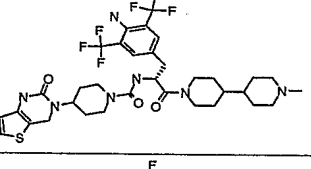
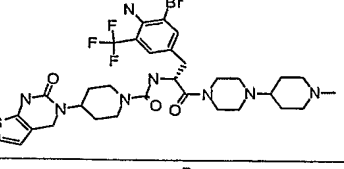
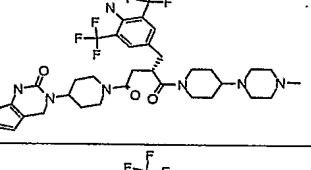
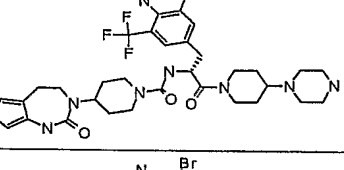
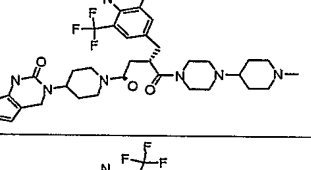
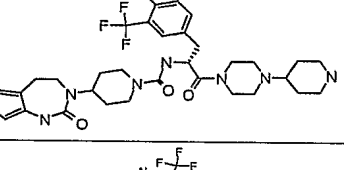
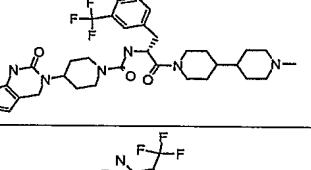
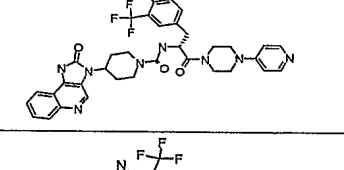
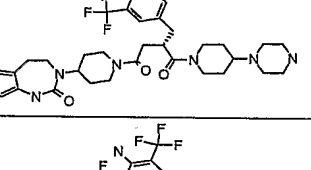
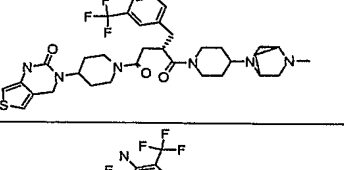
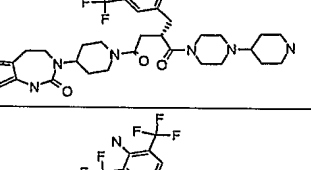
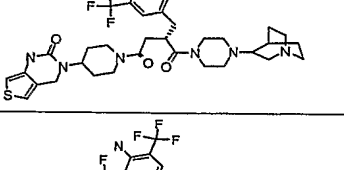
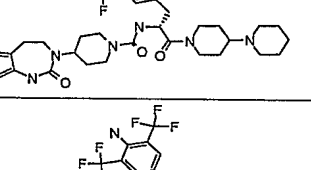
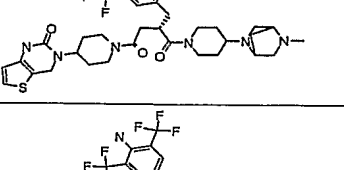
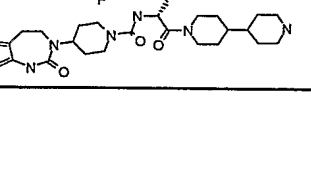
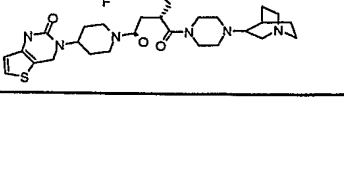
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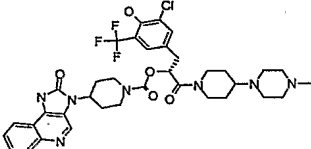
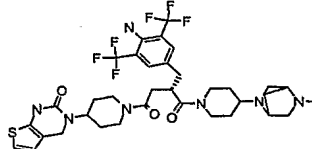
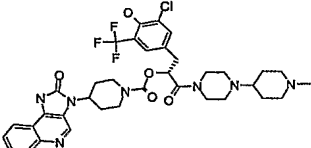
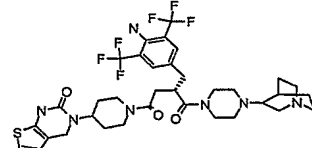
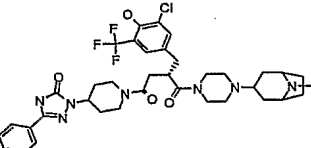
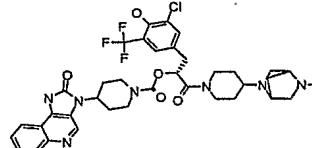
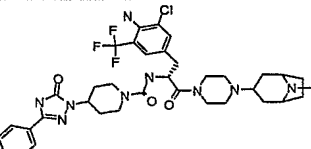
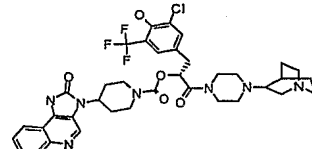
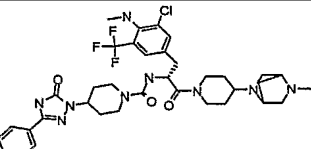
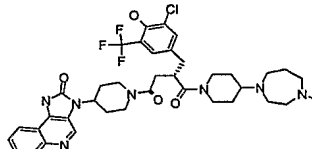
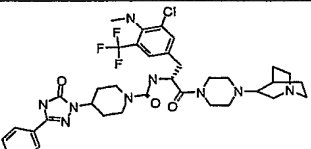
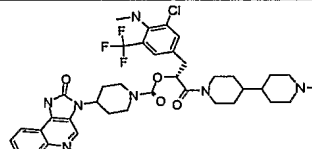
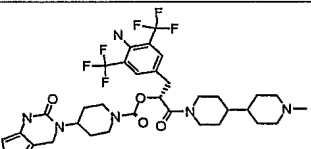
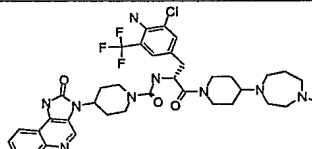
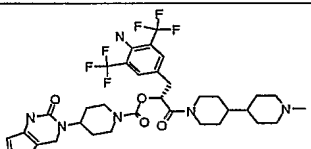
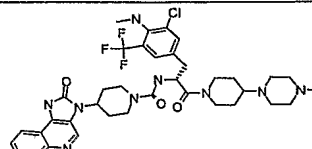
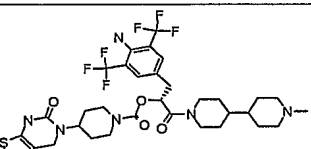
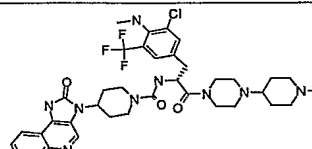
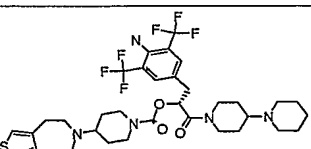
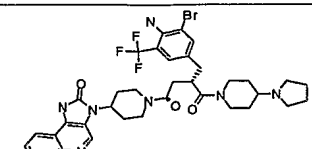
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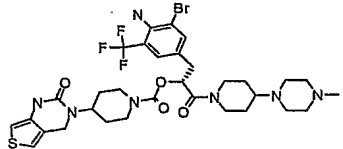
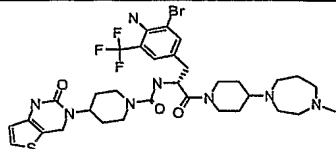
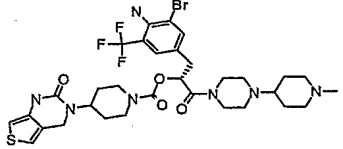
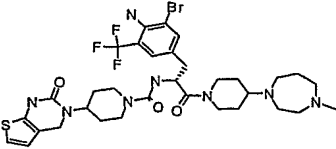
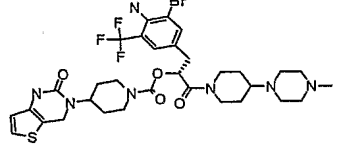
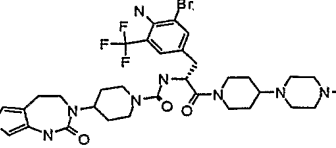
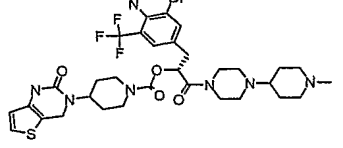
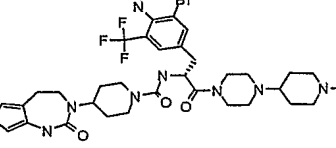
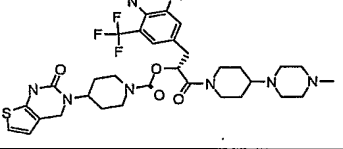
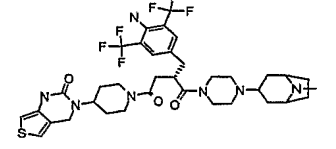
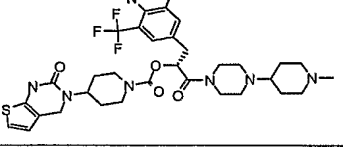
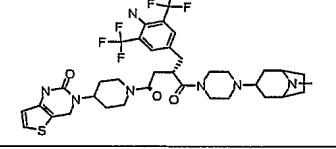
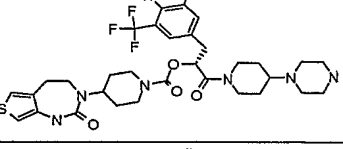
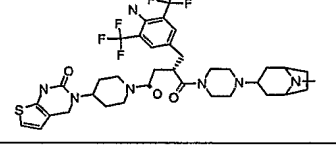
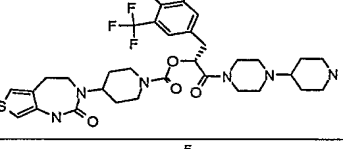
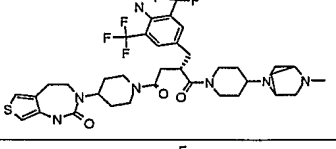
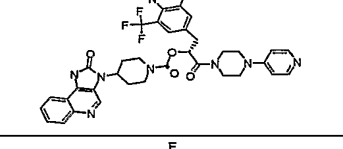
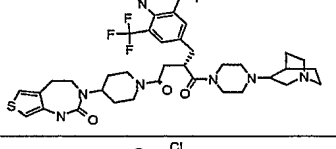
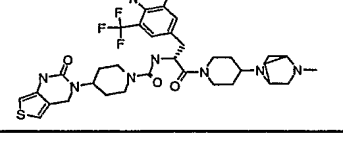
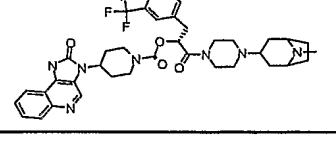
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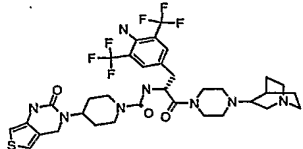
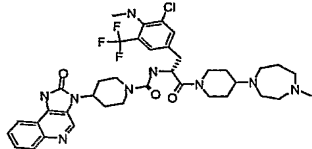
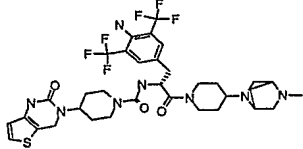
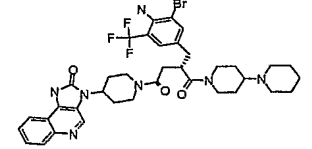
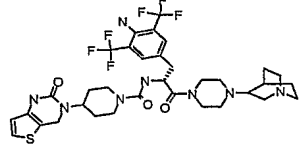
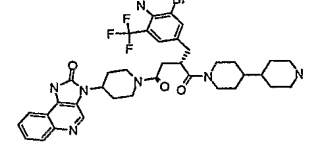
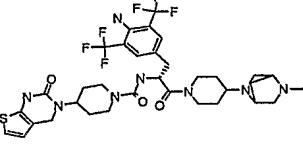
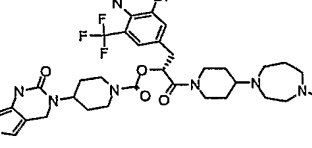
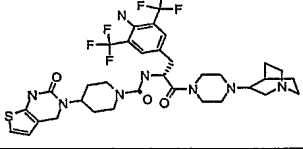
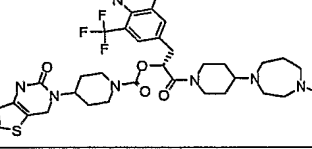
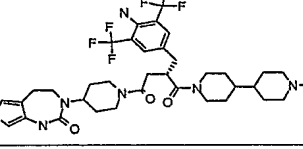
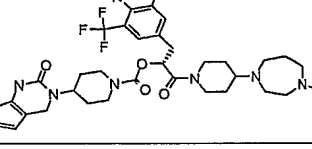
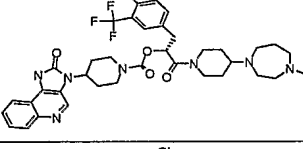
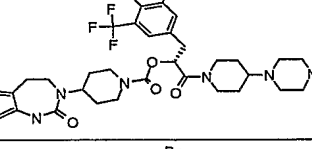
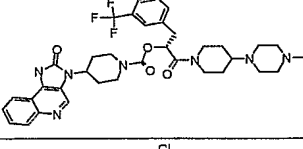
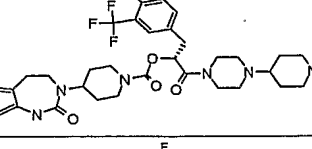
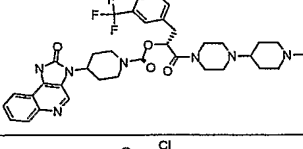
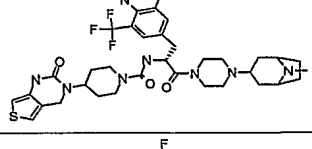
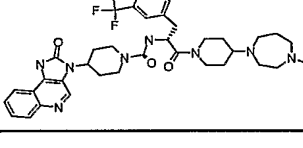
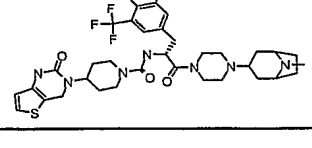
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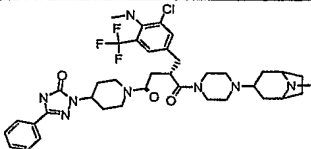
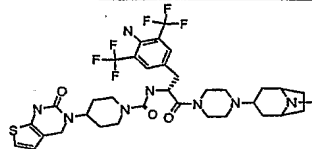
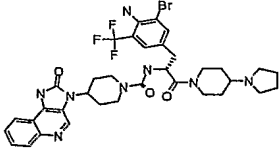
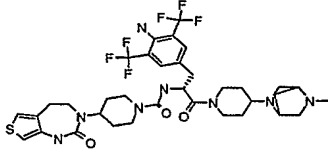
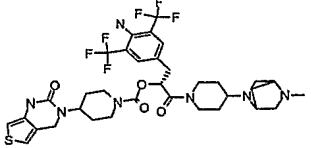
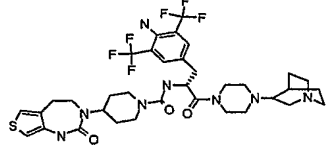
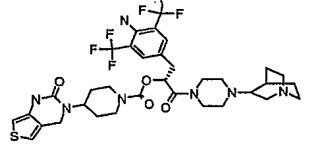
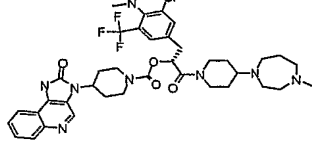
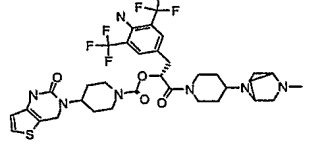
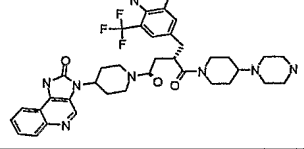
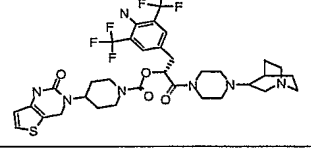
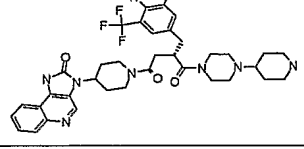
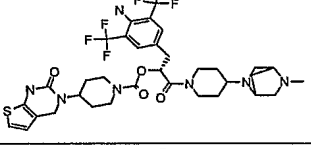
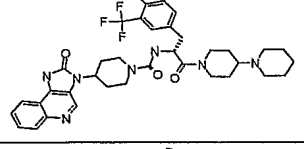
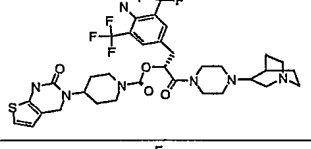
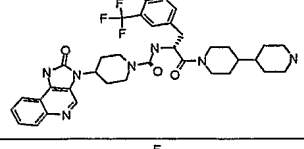
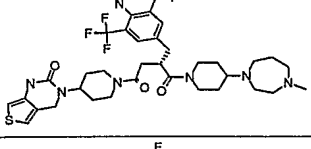
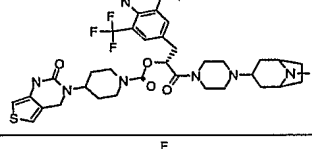
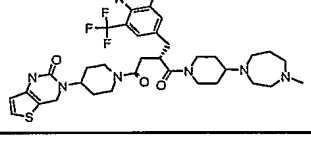
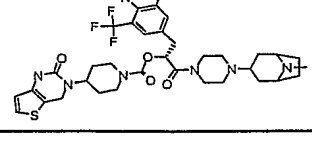
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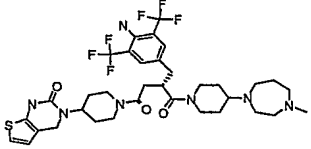
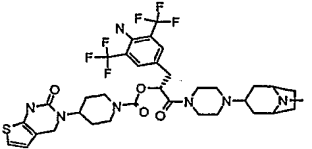
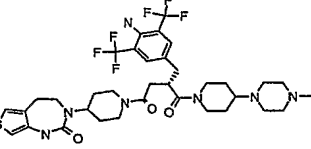
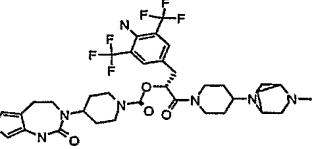
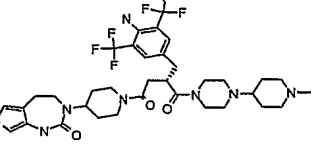
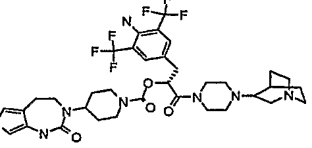
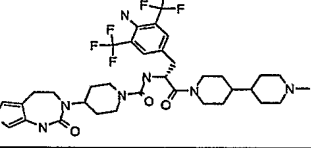
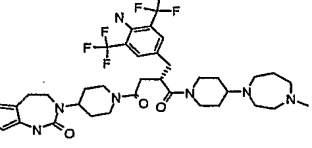
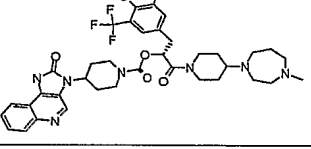
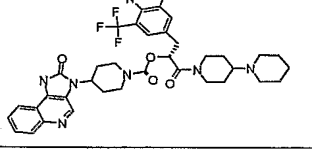
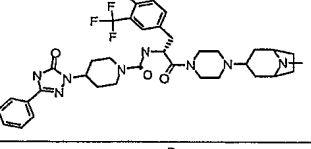
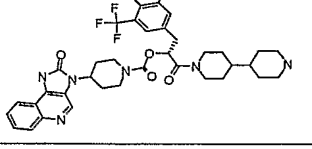
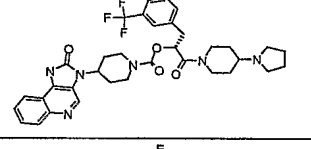
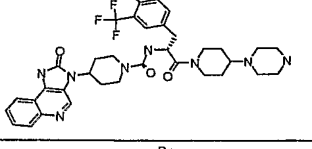
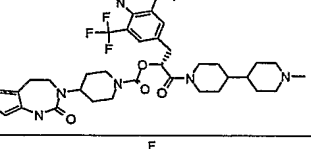
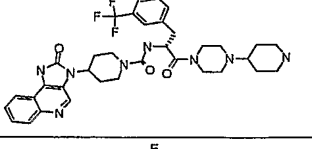
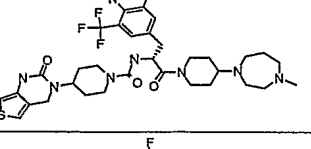
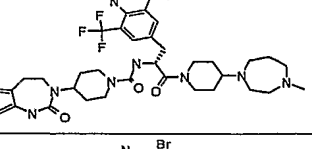
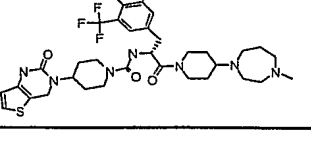
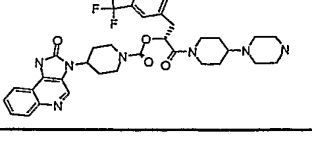
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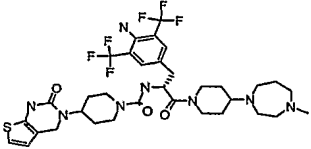
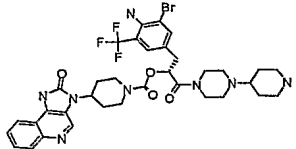
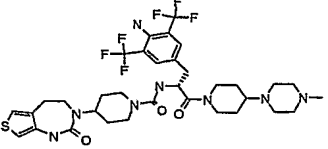
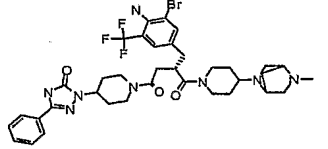
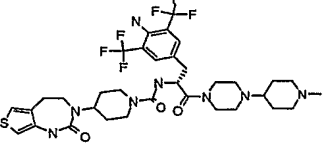
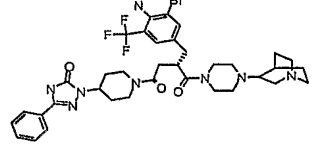
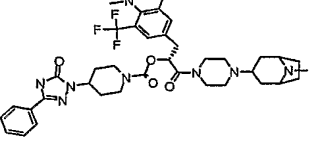
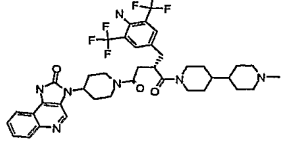
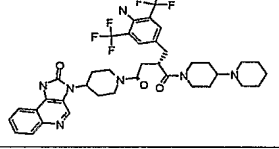
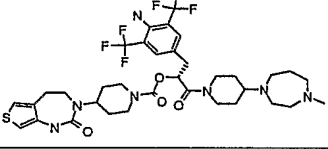
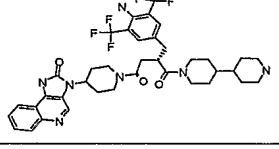
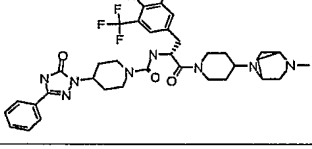
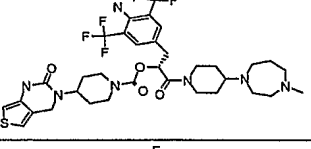
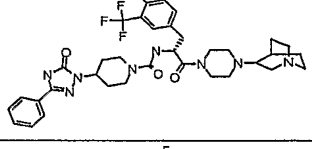
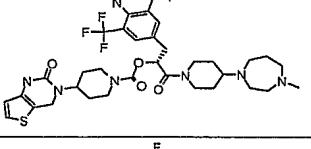
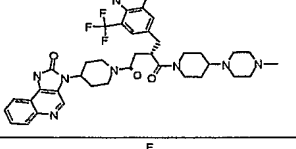
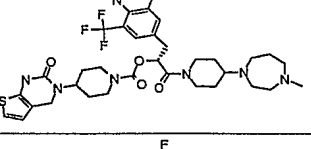
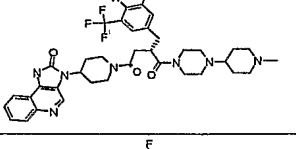
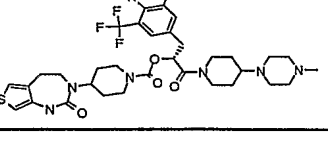
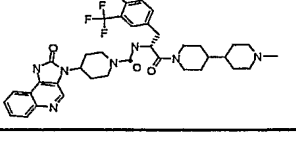
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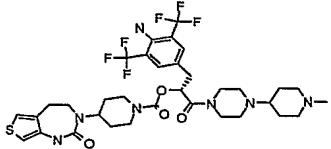
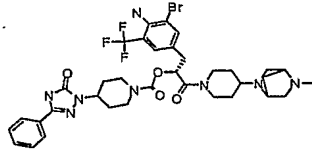
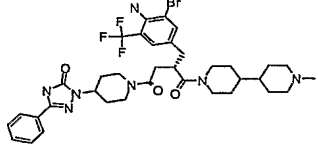
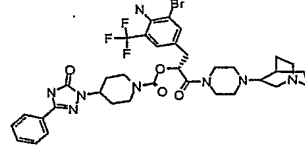
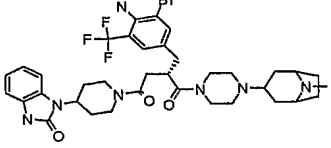
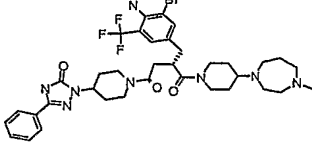
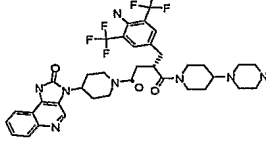
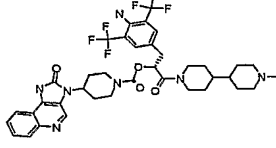
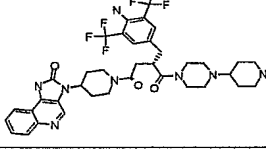
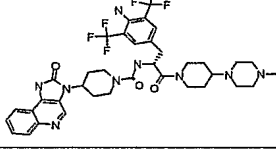
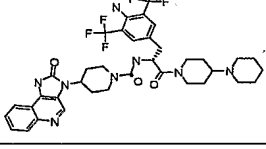
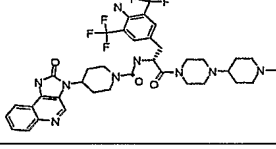
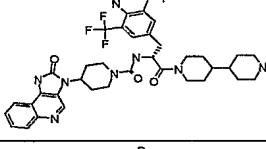
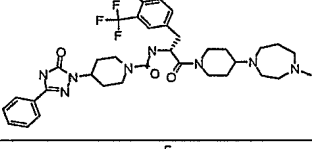
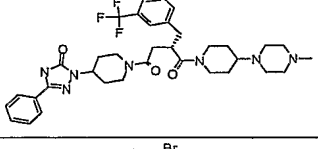
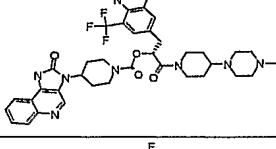
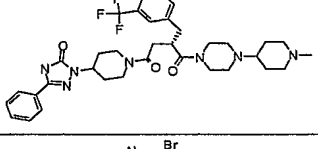
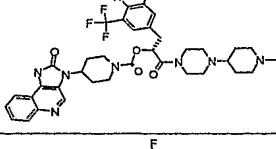
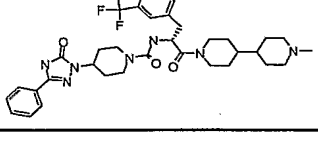
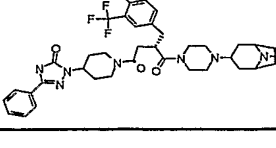
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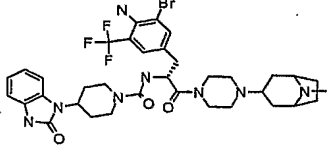
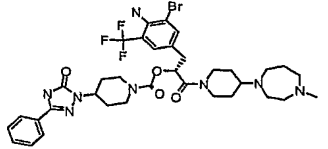
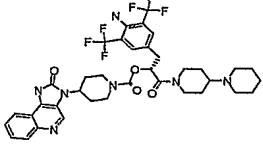
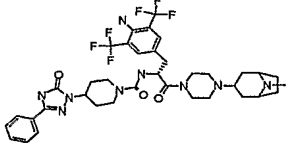
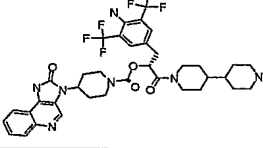
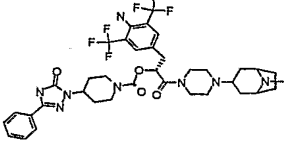
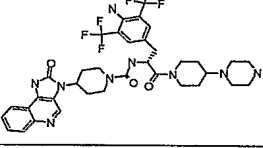
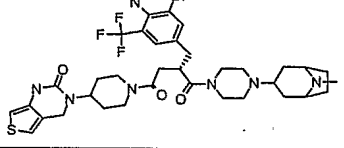
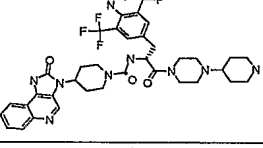
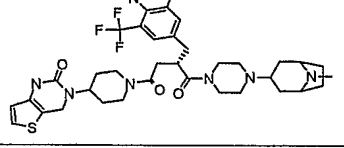
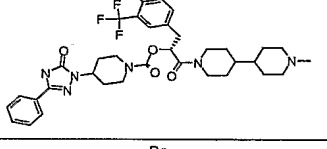
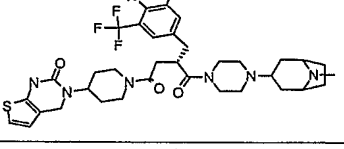
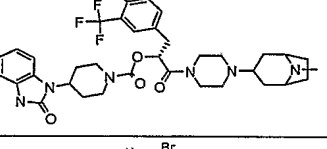
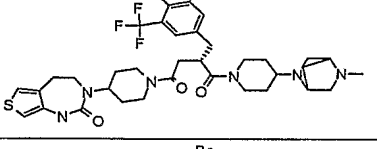
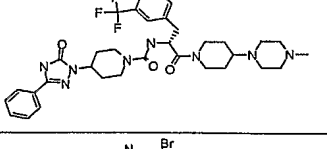
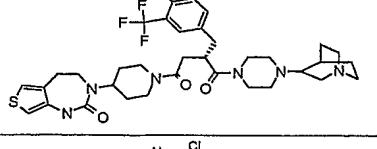
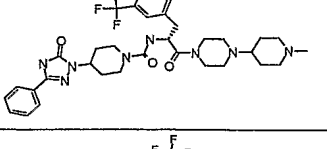
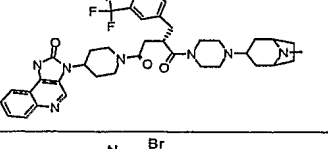
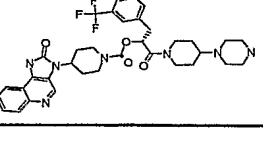
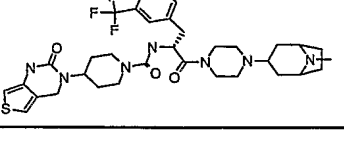
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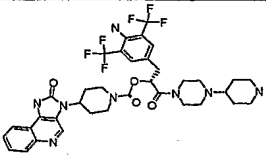
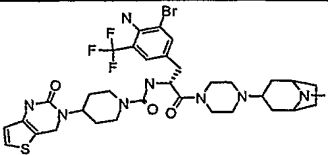
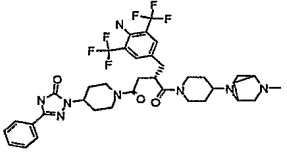
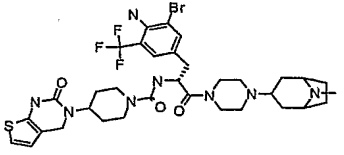
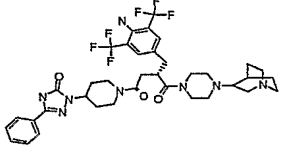
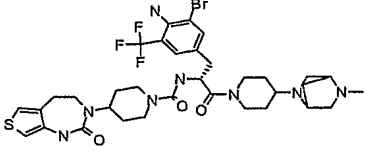
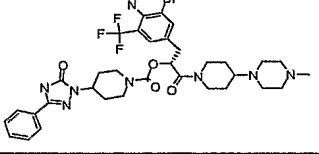
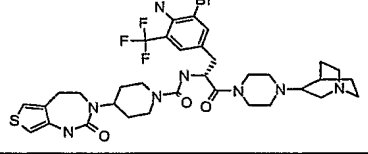
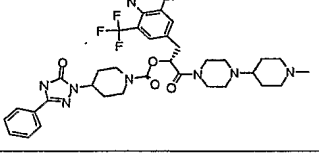
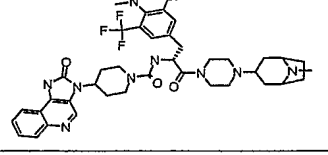
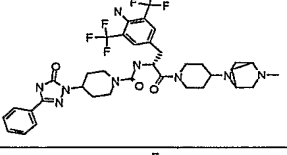
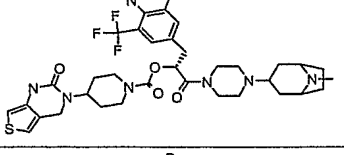
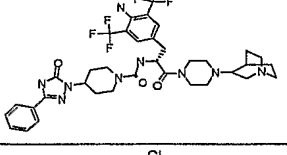
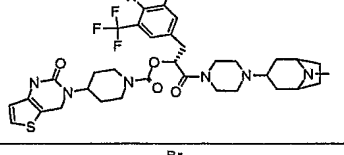
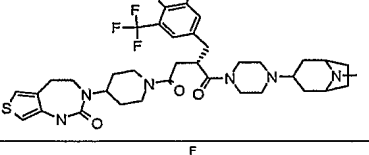
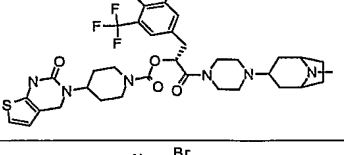
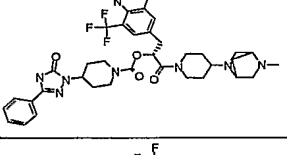
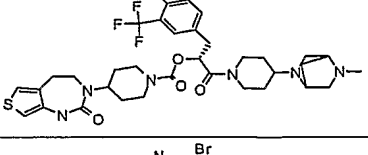
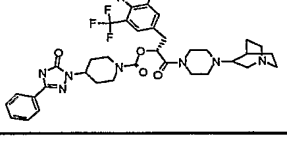
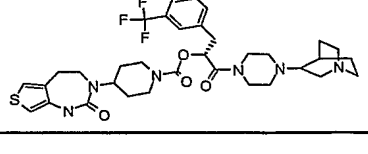
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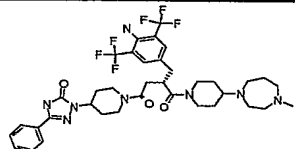
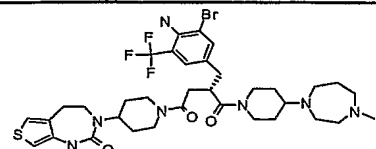
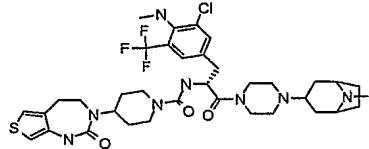
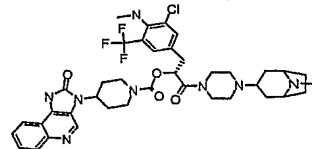
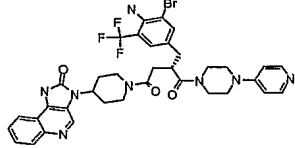
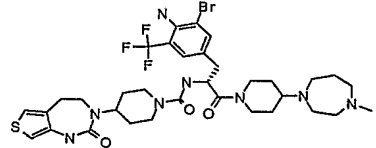
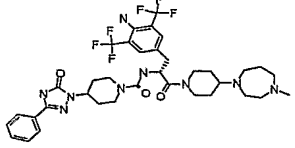
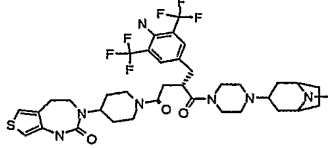
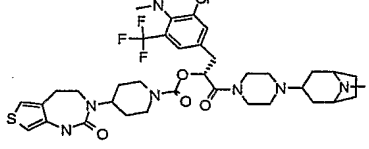
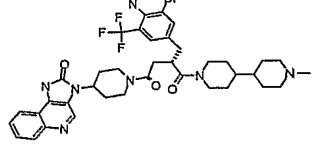
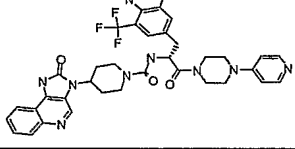
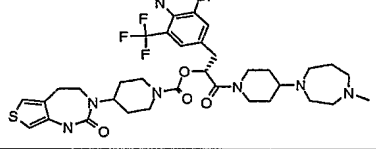
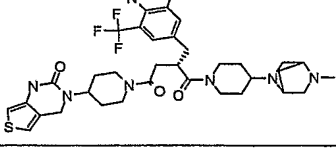
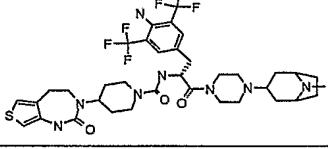
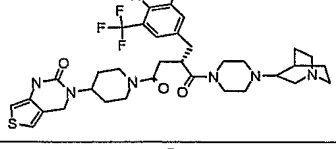
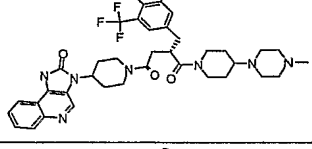
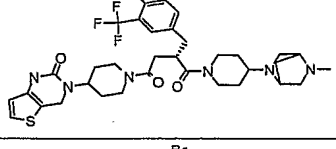
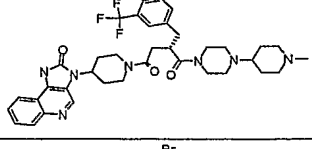
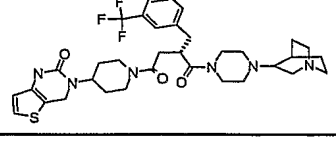
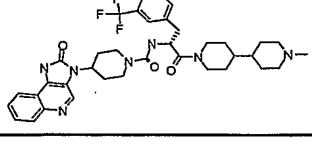
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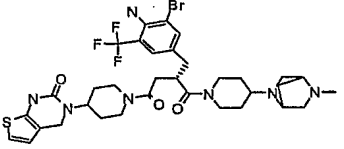
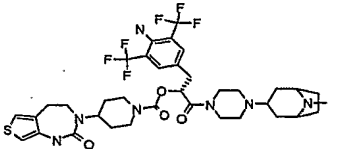
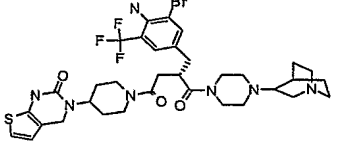
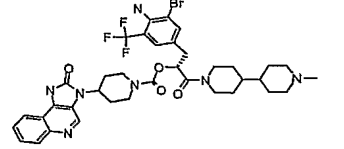
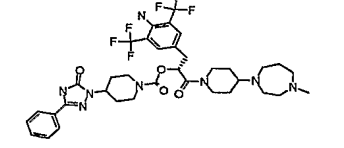
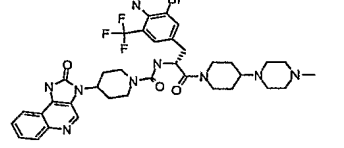
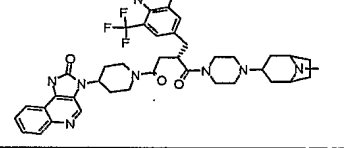
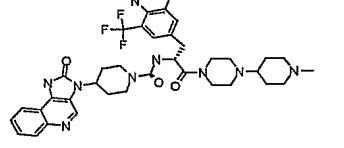
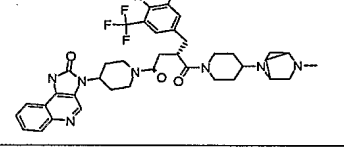
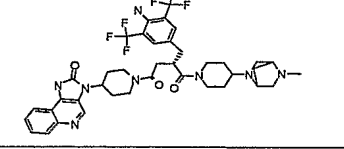
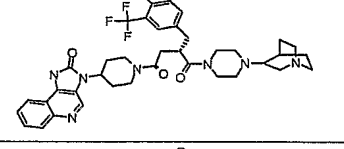
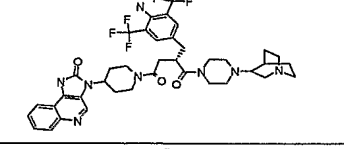
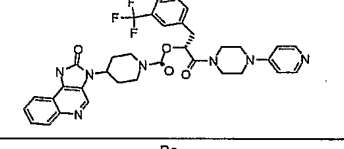
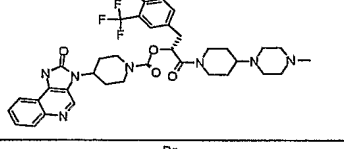
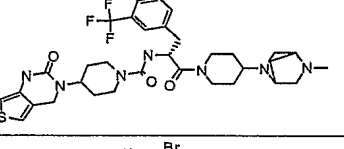
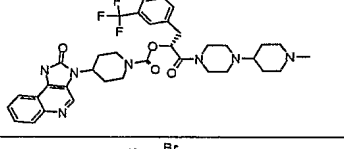
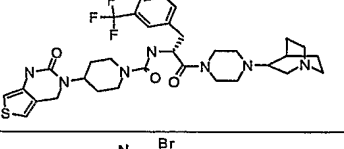
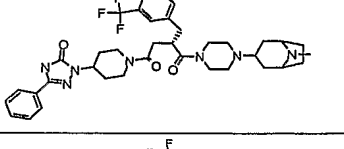
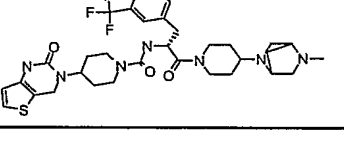
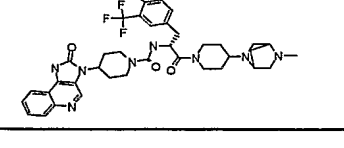
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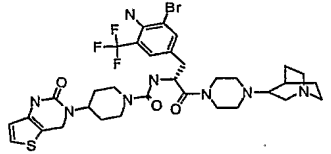
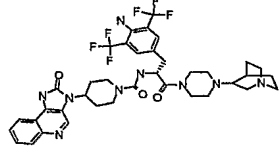
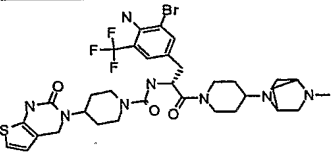
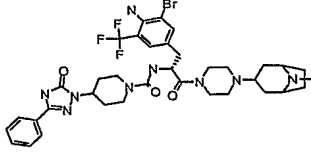
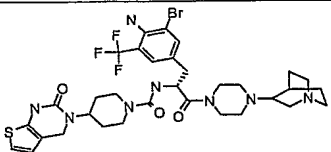
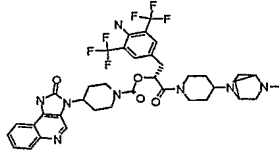
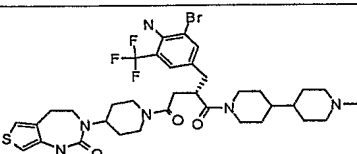
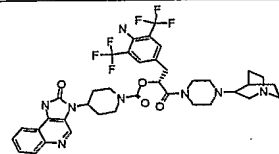
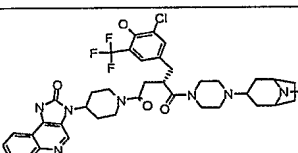
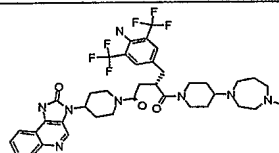
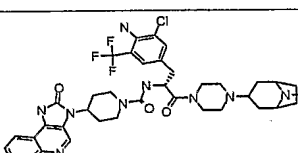
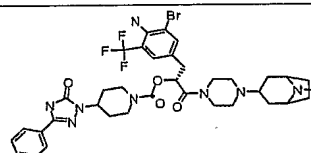
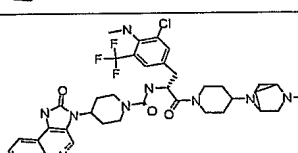
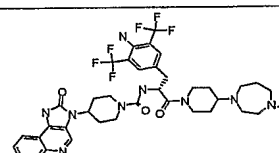
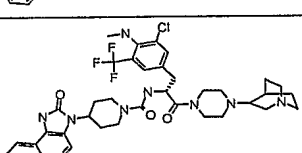
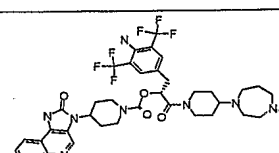
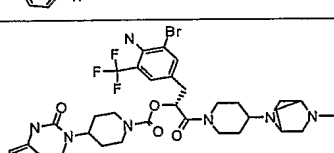
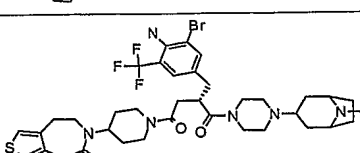
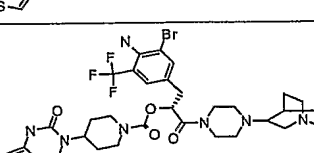
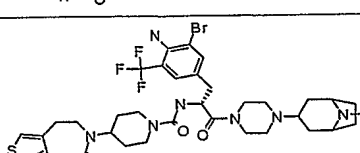
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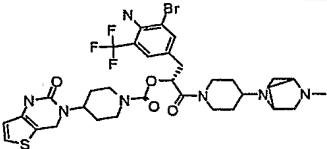
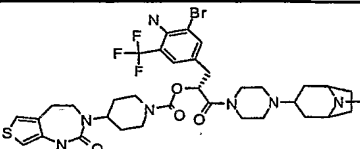
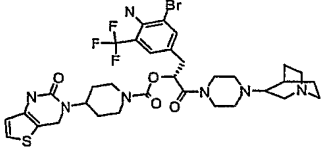
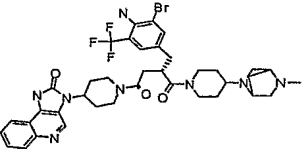
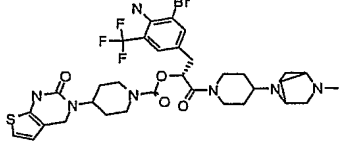
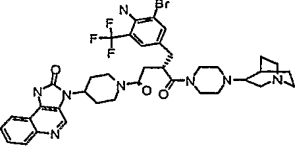
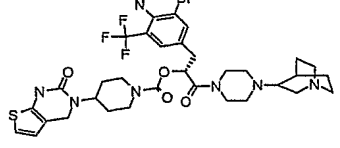
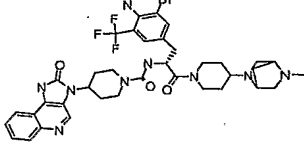
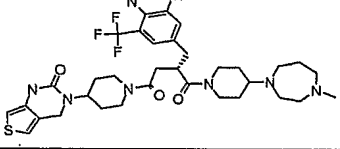
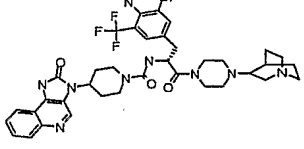
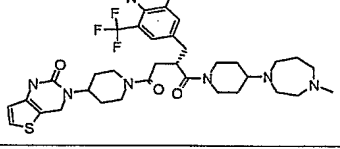
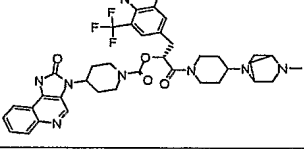
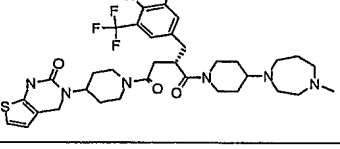
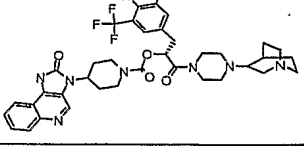
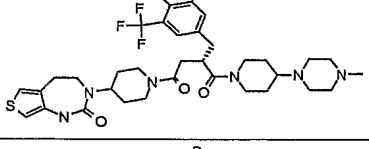
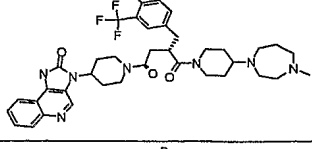
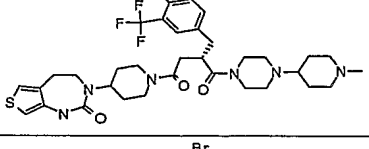
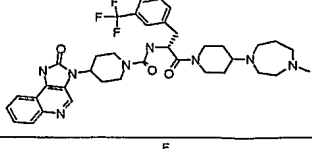
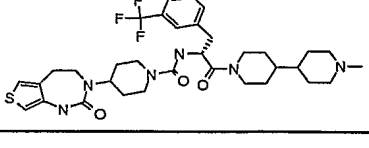
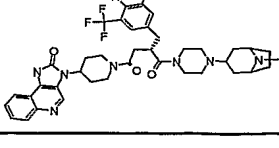
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deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze, wobei den Verbindungen

5

(1) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester,

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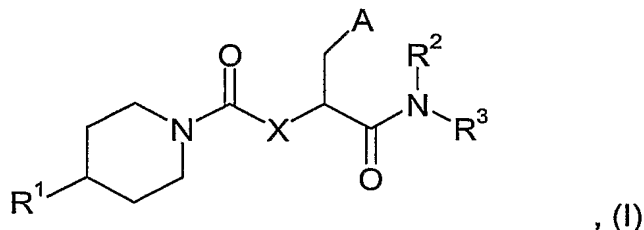
(2) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,

- (3) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,
- (4) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethylester,
- (5) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,
- (6) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,
- (7) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethylester,
- (8) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester,
- (9) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester,

deren Tautomeren, deren Diastereomeren, deren Enantiomeren, deren Hydraten, deren Gemischen und deren Salzen sowie den Hydraten der Salze eine herausragende Bedeutung zukommt.

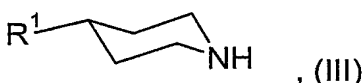
Die Verbindungen der allgemeinen Formel (I) werden nach prinzipiell bekannten Methoden hergestellt. Die folgenden Verfahren haben sich zur Herstellung der erfindungsgemäßen Verbindungen der allgemeinen Formel (I) besonders bewährt:

- 5 (a) Zur Herstellung von Verbindungen der allgemeinen Formel



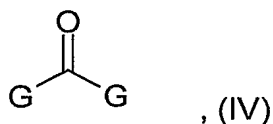
in der X das Sauerstoffatom oder die NH-Gruppe bedeutet und A und R¹ bis R³ wie  
 0 eingangs erwähnt definiert sind:

Umsetzung eines Piperidins der allgemeinen Formel



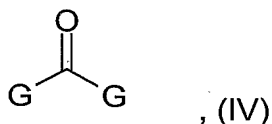
5 in der R¹ wie eingangs erwähnt definiert ist,

- (i) mit einem Kohlensäurederivat der allgemeinen Formel



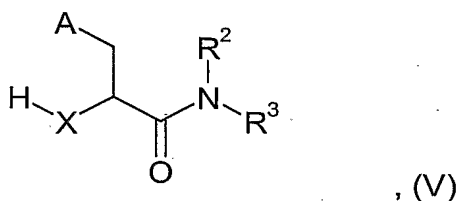
in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bevorzugt die Phenoxy-, 1H-Imidazol-1-yl-, 1H-1,2,4-Triazol-1-yl-, Trichlor-methoxy- oder die 2,5-Dioxopyrrolidin-1-yloxy-Gruppe, bedeutet, mit der  
 5 Maßgabe, dass X die NH-Gruppe darstellt, oder

- (ii) mit einem Kohlensäurederivat der allgemeinen Formel



in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann,  
 5 bevorzugt das Chloratom, die *p*-Nitrophenoxy- oder Trichlormethoxy-Gruppe,  
 bedeutet, mit der Maßgabe, dass X das Sauerstoffatom bedeutet,

und mit einer Verbindung der allgemeinen Formel



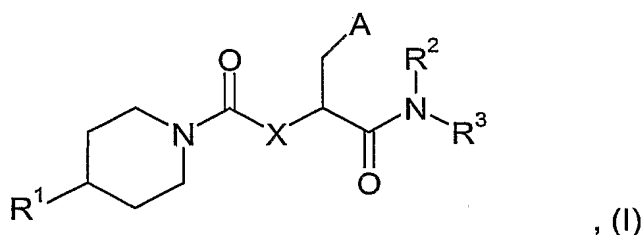
in der X das Sauerstoffatom oder eine NH-Gruppe bedeutet und A, R<sup>2</sup> und R<sup>3</sup> wie  
 eingangs erwähnt definiert sind, mit der Maßgabe, dass R<sup>2</sup> und R<sup>3</sup> keine weitere freie  
 primäre oder sekundäre aliphatische Aminofunktion enthalten.

15 Eine gegebenenfalls in dem Rest -NR<sup>2</sup>R<sup>3</sup> zusätzlich vorhandene primäre oder  
 sekundäre Aminofunktion wird jeweils mit einer geeigneten Schutzgruppe versehen.

Die im Prinzip zweistufigen Reaktionen werden in der Regel als Eintopfverfahren  
 durchgeführt, und zwar bevorzugt in der Weise, dass man in der ersten Stufe eine  
 20 der beiden Komponenten (III) oder (V) mit äquimolaren Mengen des Kohlensäure-  
 derivatives der allgemeinen Formel (IV) in einem geeigneten Lösemittel bei tieferer  
 Temperatur zur Reaktion bringt, anschließend wenigstens äquimolare Mengen der  
 anderen Komponente (III) oder (V) zugibt und die Umsetzung bei höherer  
 Temperatur beendet. Die Umsetzungen mit Bis-(trichlormethyl)-carbonat werden  
 25 bevorzugt in Gegenwart von wenigstens 2 Äquivalenten (bezogen auf Bis-  
 (trichlormethyl)-carbonat) einer tertiären Base, beispielsweise von Triethylamin,  
*N*-Ethyl-diisopropylamin, Pyridin, 1,5-Diaza-bicyclo-[4.3.0]-non-5-en, 1,4-Diazabicyclo-  
 [2.2.2]octan oder 1,8-Diazabicyclo-[5.4.0]-un-dec-7-en, durchgeführt. Als Lösungs-  
 mittel, die wasserfrei sein sollten, kommen beispielsweise Tetrahydrofuran, Dioxan,

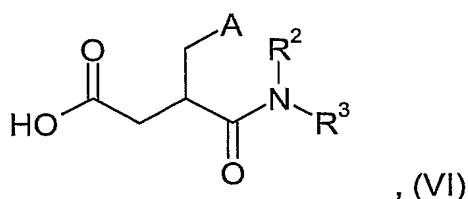
Dimethylformamid, Dimethylacetamid, N-Methyl-2-pyrrolidon, 1,3-Dimethyl-2-imidazolidinon oder Acetonitril in Betracht, bei Verwendung von Bis-(trichlormethyl)-carbonat als Carbonylkomponente werden wasserfreie Chlorkohlenwasserstoffe, beispielsweise Dichlormethan, 1,2-Dichlorethan oder Trichlorethylen, bevorzugt. Die  
5 Reaktionstemperaturen liegen für die erste Reaktionsstufe zwischen  $-30^{\circ}\text{C}$  und  $+25^{\circ}\text{C}$ , bevorzugt  $-5^{\circ}\text{C}$  und  $+10^{\circ}\text{C}$ , für die zweite Reaktionsstufe zwischen  $+15^{\circ}\text{C}$  und der Siedetemperatur des verwendeten Lösemittels, bevorzugt zwischen  $+20^{\circ}\text{C}$  und  $+70^{\circ}\text{C}$  (Siehe auch: H. A. Staab und W. Rohr, "Synthesen mit heterocyclischen Amiden (Azoliden)", Neuere Methoden der Präparativen Organischen Chemie, Band  
10 V, S. 53-93, Verlag Chemie, Weinheim/Bergstr., 1967; P. Majer und R.S. Randad, J. Org. Chem. 59, S. 1937-1938 (1994); K. Takeda, Y. Akagi, A. Saiki, T. Sukahara und H. Ogura, Tetrahedron Letters 24 (42), 4569-4572 (1983); S.R. Sandler und W. Karo in "Organic Functional Group Preparations", Vol. II, S. 223-245, Academic Press, New York 1971).

15 (b) Zur Herstellung von Verbindungen der allgemeinen Formel

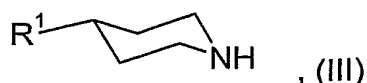


20 in der X die Methylengruppe bedeutet und A und  $\text{R}^1$  bis  $\text{R}^3$  wie eingangs erwähnt definiert sind, mit der Maßgabe, dass keine weitere freie primäre oder sekundäre aliphatische Aminofunktion im Molekül enthalten ist:

Kupplung einer Carbonsäure der allgemeinen Formel



in der A,  $R^2$  und  $R^3$  wie eingangs erwähnt definiert sind, mit einem Piperidin der allgemeinen Formel



5

in der  $R^1$  die eingangs erwähnten Bedeutungen besitzt.

Die Kupplung wird bevorzugt unter Verwendung von aus der Peptidchemie bekannten Verfahren (siehe z. B. Houben-Weyl, Methoden der Organischen Chemie, Bd. 15/2) durchgeführt, wobei zum Beispiel Carbodiimide, wie z.B. Dicyclohexylcarbodiimid (DCC), Diisopropylcarbodiimid (DIC) oder Ethyl-(3-dimethylamino-propyl)-carbodiimid, O-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorphosphat (HBTU) oder -tetrafluorborat (TBTU) oder 1*H*-Benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorphosphat (BOP) eingesetzt werden.

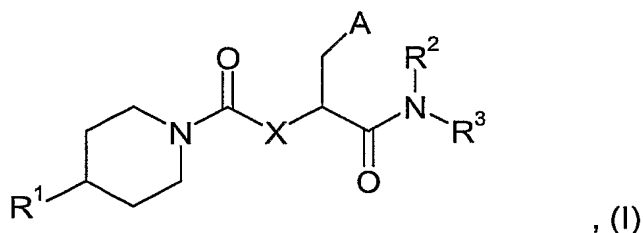
Durch Zugabe von 1-Hydroxybenzotriazol (HOBt) oder von 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazin (HOOBt) kann die Reaktionsgeschwindigkeit gesteigert werden. Die Kupplungen werden normalerweise mit äquimolaren Anteilen der Kupplungskomponenten sowie des Kupplungsreagenz in Lösemitteln wie Dichlormethan, Tetrahydrofuran, Acetonitril, Dimethylformamid (DMF), Dimethylacetamid (DMA), *N*-Methylpyrrolidon (NMP) oder Gemischen aus diesen und bei Temperaturen zwischen  $-30^{\circ}\text{C}$  und  $+30^{\circ}\text{C}$ , bevorzugt  $-20^{\circ}\text{C}$  und  $+25^{\circ}\text{C}$ , durchgeführt. Sofern erforderlich, wird als zusätzliche Hilfsbase *N*-Ethyldiisopropylamin (DIEA) (Hünig-Base) bevorzugt.

Als weiteres Kupplungsverfahren zur Synthese von Verbindungen der allgemeinen Formel (I) wird das sogenannte "Anhydridverfahren" (siehe auch: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, S. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, S. 21-27) eingesetzt. Bevorzugt wird das "gemischte Anhydridverfahren" in der Variante nach Vaughan (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), bei der unter Verwendung von Chlorkohlensäureisobutylester in Gegenwart von Basen, wie 4-Methylmorpholin oder 4-Ethylmorpholin, das gemischte Anhydrid aus der zu kuppelnden Carbonsäure der

allgemeinen Formel (VI) und dem Kohlensäure-monoisobutylester erhalten wird. Die Herstellung dieses gemischten Anhydrids und die Kupplung mit Aminen erfolgt im Eintopfverfahren, unter Verwendung der vorstehend genannten Lösemittel und bei Temperaturen zwischen -20 und +25°C, bevorzugt 0°C und +25°C.

5

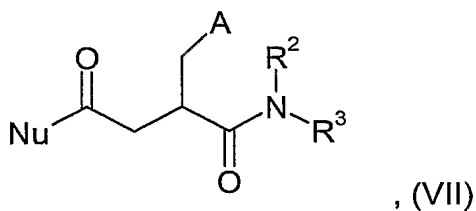
(c) Zur Herstellung von Verbindungen der allgemeinen Formel



10 in der X die Methylengruppe bedeutet und A und R² und R³ wie eingangs erwähnt definiert sind, mit der Maßgabe, dass diese Gruppen kein freies primäres oder sekundäres Amin enthalten:

Kupplung einer Verbindung der allgemeinen Formel

15



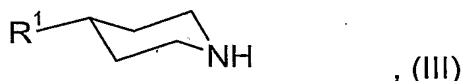
in der A, R² und R³ wie eingangs erwähnt definiert sind, mit der Maßgabe, dass R² und R³ kein freies primäres oder sekundäres Amin enthalten, und Nu eine Austrittsgruppe, beispielsweise ein Halogenatom, wie das Chlor-, Brom- oder Iodat, eine Alkylsulfonyloxygruppe mit 1 bis 10 Kohlenstoffatomen im Alkylteil, eine gegebenenfalls durch Chlor- oder Bromatome, durch Methyl- oder Nitrogruppen mono-, di- oder trisubstituierte Phenylsulfonyloxy- oder Naphthylsulfonyloxygruppe, wobei die Substituenten gleich oder verschieden sein können, eine 1H-Imidazol-1-yl-,  
 20 eine gegebenenfalls durch eine oder zwei Methylgruppen im Kohlenstoffgerüst substituierte 1H-Pyrazol-1-yl-, eine 1H-1,2,4-Triazol-1-yl-, 1H-1,2,3-Triazol-1-yl-, 1H-

25

1,2,3,4-Tetrazol-1-yl-, eine Vinyl-, Propargyl-, *p*-Nitrophenyl-, 2,4-Dinitrophenyl-, Trichlorphenyl-, Pentachlorphenyl-, Pentafluorphenyl-, Pyranyl- oder Pyridinyl-, eine Dimethylaminyloxy-, 2(1*H*)-Oxopyridin-1-yl-oxy-, 2,5-Dioxopyrrolidin-1-yloxy-, Phthalimidyl-oxy-, 1*H*-Benzo-triazol-1-yloxy- oder Azidgruppe bedeutet,

5

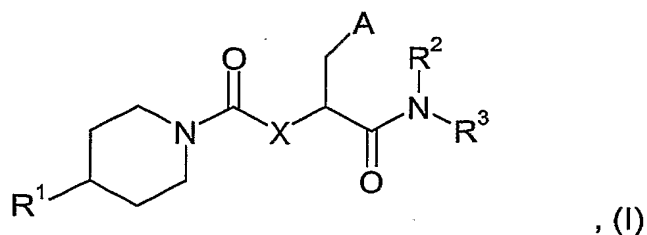
mit einem Piperidin der allgemeinen Formel



10 in der R<sup>1</sup> wie eingangs erwähnt definiert ist.

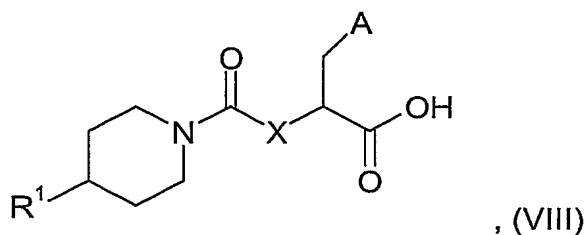
Die Umsetzung wird unter Schotten-Baumann- oder Einhorn-Bedingungen durchgeführt, das heißt die Komponenten werden in Gegenwart von wenigstens einem Äquivalent einer Hilfsbase bei Temperaturen zwischen -50°C und +120°C, bevorzugt -10°C und +30°C, und gegebenenfalls in Gegenwart von Lösemitteln zur  
15 Reaktion gebracht. Als Hilfsbasen kommen bevorzugt Alkali- und Erdalkalihydroxide, beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkalicarbonat, z. B. Natriumcarbonat, Kaliumcarbonat oder Cäsiumcarbonat, Alkaliacetate, z.B. Natrium- oder Kaliumacetat, sowie tertiäre Amine, beispielsweise  
20 Pyridin, 2,4,6-Tri-methylpyridin, Chinolin, Triethylamin, *N*-Ethyl-diisopropylamin, *N*-Ethyl-dicyclohexyl-amin, 1,4-Di-azabicyclo[2.2.2]octan oder 1,8-Diazabicyclo[5.4.0]-undec-7-en, als Lösemittel beispielsweise Dichlormethan, Tetrahydrofuran, 1,4-Dioxan, Acetonitril, Dimethylformamid, Dimethylacetamid, *N*-Methylpyrrolidon oder Gemische davon in Betracht; werden als Hilfsbasen Alkali- oder Erdalkali-  
25 hydroxide, Alkalicarbonat oder -acetate verwendet, kann dem Reaktionsgemisch auch Wasser als Cosolvens zugesetzt werden.

(d) Zur Herstellung von Verbindungen der allgemeinen Formel



in der A, X und R<sup>1</sup> bis R<sup>3</sup> wie eingangs erwähnt definiert sind:

5 Kupplung einer Carbonsäure der allgemeinen Formel



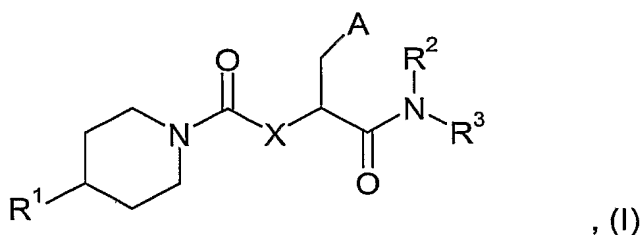
in der A, X und R<sup>1</sup> wie eingangs erwähnt definiert sind, mit einem Amin der  
 0 allgemeinen Formel HNR<sup>2</sup>R<sup>3</sup>, in der R<sup>2</sup> und R<sup>3</sup> wie eingangs definiert sind, mit der  
 Maßgabe, dass sie keine weitere freie primäre oder sekundäre aliphatische  
 Aminofunktion enthalten.

Die Kupplung wird bevorzugt unter Verwendung von aus der Peptidchemie bekann-  
 5 ten Verfahren (siehe z. B. Houben-Weyl, Methoden der Organischen Chemie, Band  
 15/2) durchgeführt, wobei zum Beispiel Carbodiimide, wie z.B. Dicyclohexylcarbo-  
 diimid (DCC), Diisopropylcarbodiimid (DIC) oder Ethyl-(3-dimethylamino-propyl)-  
 carbodiimid, O-(1*H*-Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium-hexafluorphos-  
 phat (HBTU) oder -tetrafluorborat (TBTU) oder 1*H*-Benzotriazol-1-yl-oxy-tris-  
 20 (dimethylamino)-phosphoniumhexafluorphosphat (BOP) eingesetzt werden. Durch  
 Zugabe von 1-Hydroxybenzotriazol (HOBt) oder von 3-Hydroxy-4-oxo-3,4-dihydro-  
 1,2,3-benzotriazin (HOObt) kann die Reaktionsgeschwindigkeit gesteigert werden.  
 Die Kupplungen werden normalerweise mit äquimolaren Anteilen der Kupplungs-  
 komponenten sowie des Kupplungsreagenz in Lösungsmitteln wie Dichlormethan,  
 25 Tetrahydrofuran, Acetonitril, Dimethylformamid (DMF), Dimethylacetamid (DMA),  
*N*-Methylpyrrolidon (NMP) oder Gemischen aus diesen und bei Temperaturen

zwischen -30 und +30°C, bevorzugt -20 und +25°C, durchgeführt. Sofern erforderlich wird als zusätzliche Hilfsbase *N*-Ethyl-diisopropylamin (DIEA) (Hünig-Base) bevorzugt.

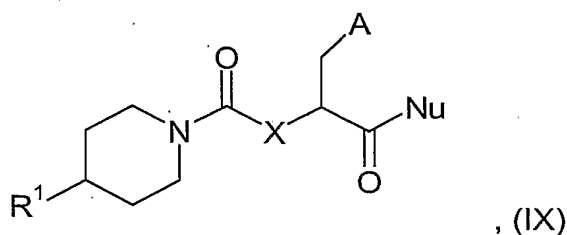
- 5 Als weiteres Kupplungsverfahren zur Synthese von Verbindungen der allgemeinen Formel (I) wird das sogenannte "Anhydridverfahren" (siehe auch: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, S. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, S. 21-27) eingesetzt. Bevorzugt wird das
- 0 "gemischte Anhydridverfahren" in der Variante nach Vaughan (J.R. Vaughan Jr., J. Amer. Chem.Soc. 73, 3547 (1951)), bei der unter Verwendung von Chlorkohlensäureisobutylester in Gegenwart von Basen, wie 4-Methylmorpholin oder 4-Ethylmorpholin, das gemischte Anhydrid aus der zu kuppelnden Carbonsäure der allgemeinen Formel (VIII) und dem Kohlensäuremonoisobutylester erhalten wird. Die Herstellung
- 5 dieses gemischten Anhydrids und die Kupplung mit den Aminen der allgemeinen Formel  $\text{HNR}^2\text{R}^3$  erfolgt im Eintopfverfahren, unter Verwendung der vorstehend genannten Lösemittel und bei Temperaturen zwischen -20°C und +25°C, bevorzugt zwischen 0°C und +25°C.

(e) Zur Herstellung von Verbindungen der allgemeinen Formel



in der A, X und  $\text{R}^1$  bis  $\text{R}^3$  wie eingangs erwähnt definiert sind, mit der Maßgabe, dass kein freies primäres oder sekundäres Amin im Molekül enthalten ist:

Kupplung einer Verbindung der allgemeinen Formel



in der A, X und R<sup>1</sup> wie eingangs erwähnt definiert sind und Nu eine Austrittsgruppe, beispielsweise ein Halogenatom, wie das Chlor-, Brom- oder Iodat, eine Alkylsulfonyloxygruppe mit 1 bis 10 Kohlenstoffatomen im Alkylteil, eine gegebenenfalls durch Chlor- oder Bromatome, durch Methyl- oder Nitrogruppen mono-, di- oder trisubstituierte Phenylsulfonyloxy- oder Naphthylsulfonyloxygruppe, wobei die Substituenten gleich oder verschieden sein können, eine 1H-Imidazol-1-yl-, eine gegebenenfalls durch eine oder zwei Methylgruppen im Kohlenstoffgerüst substituier-  
 10 te 1H-Pyrazol-1-yl-, eine 1H-1,2,4-Triazol-1-yl-, 1H-1,2,3-Triazol-1-yl-, 1H-1,2,3,4-Tetrazol-1-yl-, eine Vinyl-, Propargyl-, p-Nitrophenyl-, 2,4-Dinitrophenyl-, Trichlorphenyl-, Pentachlorphenyl-, Pentafluorphenyl-, Pyran- oder Pyridin-yl-, eine Dimethylaminyloxy-, 2(1H)-Oxopyridin-1-yl-oxy-, 2,5-Dioxopyrrolidin-1-yloxy-, Phthalimidyloxy-, 1H-Benzo-triazol-1-yloxy- oder Azidgruppe bedeutet,

15 mit einem Amin der allgemeinen Formel HNR<sup>2</sup>R<sup>3</sup>, in der R<sup>2</sup> und R<sup>3</sup> wie eingangs definiert sind, mit der Maßgabe, dass keine freie Carbonsäure- und/oder keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten ist.

20 Die Umsetzung wird unter Schotten-Baumann- oder Einhorn-Bedingungen durchgeführt, das heißt, die Komponenten werden in Gegenwart von wenigstens einem Äquivalent einer Hilfsbase bei Temperaturen zwischen -50°C und +120°C, bevorzugt -10°C und +30°C, und gegebenenfalls in Gegenwart von Lösungsmitteln zur Reaktion gebracht. Als Hilfsbasen kommen bevorzugt Alkali- und Erdalkalihydroxide, beispielsweise Natriumhydroxid, Kaliumhydroxid oder Bariumhydroxid, Alkali-  
 25 carbonate, z. B. Natriumcarbonat, Kaliumcarbonat oder Cäsiumcarbonat, Alkaliacetate, z.B. Natrium- oder Kaliumacetat, sowie tertiäre Amine, beispielsweise Pyridin, 2,4,6-Trimethylpyridin, Chinolin, Triethylamin, N-Ethyl-diisopropylamin, N-Ethyl-dicyclohexylamin, 1,4-Di-azabicyclo[2.2.2]octan oder 1,8-Diaza-bicyclo[5.4.0]-  
 30 undec-7-en, als Lösungsmittel beispielsweise Dichlormethan, Tetrahydrofuran,

1,4-Dioxan, Acetonitril, Dimethylformamid, Dimethylacetamid, *N*-Methylpyrrolidon oder Gemische davon in Betracht; werden als Hilfsbasen Alkali- oder Erdalkalihydroxide, Alkalicarbonat oder -acetate verwendet, kann dem Reaktionsgemisch auch Wasser als Cosolvens zugesetzt werden.

5

Die erfindungsgemäßen neuen Verbindungen der allgemeinen Formel (I) enthalten ein oder mehrere Chiralitätszentren. Sind beispielsweise zwei Chiralitätszentren vorhanden, dann können die Verbindungen in Form zweier diastereomerer Antipodenpaare auftreten. Die Erfindung umfaßt die einzelnen Isomeren ebenso wie ihre  
10 Gemische.

Die Trennung der jeweiligen Diastereomeren gelingt auf Grund ihrer unterschiedlichen physikochemischen Eigenschaften, z.B. durch fraktionierte Kristallisation aus geeigneten Lösemitteln, durch Hochdruckflüssigkeits- oder Säulenchromatographie  
15 unter Verwendung chiraler oder bevorzugt achiraler stationärer Phasen.

Die Trennung von unter die allgemeine Formel (I) fallenden Racematen gelingt beispielsweise durch HPLC an geeigneten chiralen stationären Phasen (z. B. Chiral AGP, Chiralpak AD). Racemate, die eine basische Funktion enthalten, lassen sich  
20 auch über die diastereomeren, optisch aktiven Salze trennen, die bei Umsetzung mit einer optisch aktiven Säure, beispielsweise (+)- oder (-)-Weinsäure, (+)- oder (-)-Diacetylweinsäure, (+)- oder (-)-Monomethyltartrat oder (+)-Camphersulfonsäure entstehen.

25 Nach einem üblichen Verfahren zur Isomerentrennung wird das Racemat einer Verbindung der allgemeinen Formel (I) mit einer der vorstehend angegebenen optisch aktiven Säuren in äquimolarer Menge in einem Lösemittel umgesetzt und die erhaltenen kristallinen, diastereomeren, optisch aktiven Salze unter Ausnutzung ihrer verschiedenen Löslichkeit getrennt. Diese Umsetzung kann in jeder Art von  
30 Lösemitteln durchgeführt werden, solange sie einen ausreichenden Unterschied hinsichtlich der Löslichkeit der Salze aufweisen. Vorzugsweise werden Methanol, Ethanol oder deren Gemische, beispielsweise im Volumenverhältnis 50:50, verwendet. Sodann wird jedes der optisch aktiven Salze in Wasser gelöst, mit einer

Base, wie Natriumcarbonat oder Kaliumcarbonat, oder mit einer geeigneten Säure, beispielsweise mit verdünnter Salzsäure oder wässriger Methansulfonsäure, vorsichtig neutralisiert und dadurch die entsprechende freie Verbindung in der (+)- oder (-)-Form erhalten.

5

Jeweils nur das (*R*)- oder (*S*)-Enantiomer bzw. ein Gemisch zweier optisch aktiver, unter die allgemeine Formel (I) fallender diastereomerer Verbindungen wird auch dadurch erhalten, dass man die oben beschriebenen Synthesen mit jeweils einer geeigneten (*R*)- bzw. (*S*)-konfigurierten Reaktionskomponente durchführt.

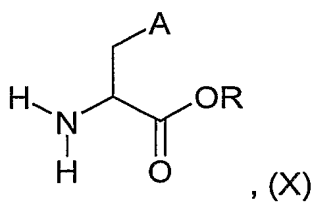
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Die Ausgangsverbindungen der allgemeinen Formel (III) erhält man, soweit sie nicht literaturbekannt oder gar käuflich sind, entsprechend den in der internationalen Patentanmeldung WO 98/11128 und DE 199 52 146 angegebenen Verfahren. Die Ausgangsverbindungen der allgemeinen Formel (IV) sind käuflich. Verbindungen der allgemeinen Formel (V) lassen sich nach dem Peptidchemiker geläufigen Methoden aus geschützten Phenylalaninen und Aminen der allgemeinen Formel  $\text{HNR}^2\text{R}^3$  herstellen.

5

Die zur Herstellung der optisch reinen Verbindungen der allgemeinen Formel (V) nötigen Phenylalaninderivate können aus den Verbindungen der allgemeinen Formel

0



in der A wie eingangs erwähnt definiert ist und R eine unverzweigte Alkylgruppe, bevorzugt die Methyl- oder Ethylgruppe, darstellt, durch Racematspaltung hergestellt werden.

5

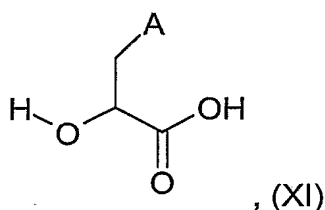
Diese Racematspaltung kann mit Hilfe enzymatischer Methoden durchgeführt werden, wobei nur ein Enantiomer des Racemates transformiert wird und das entstehende Gemisch dann mit Hilfe physikochemischer Methoden, bevorzugt mit

0

Hilfe chromatographischer Methoden, getrennt wird. Ein geeignetes Enzymsystem für diesen Schritt stellt das Enzym Alcalase 2.4 L FG (Novozymes A/S; DK 2880 Bagsvaerd) dar. Die Verbindungen der allgemeinen Formel (X) können dann mit für Peptidchemiker geläufigen Methoden in die enantiomerenreinen Verbindungen der allgemeinen Formel (V) überführt werden.

Falls die Gruppe X in Verbindungen der allgemeinen Formel (V) das Sauerstoffatom darstellt, können die für die Synthese benötigten Hydroxycarbonsäuren der allgemeinen Formel

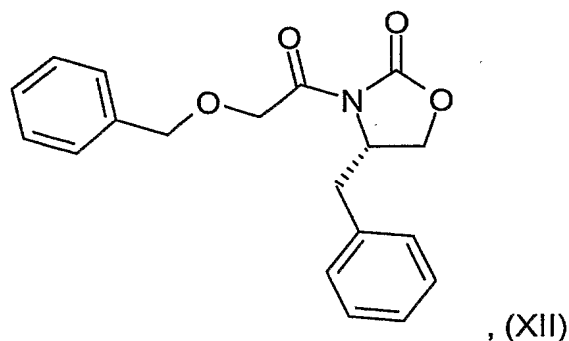
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in der A wie eingangs erwähnt definiert ist, aus Verbindungen der allgemeinen Formel (X) gewonnen werden, mit der Maßgabe, dass R das Wasserstoffatom darstellt.

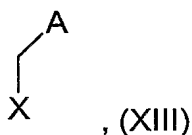
Unter der Maßgabe, dass der Rest A keine Amino- oder Methylaminogruppe enthält, können durch Diazotierung von Verbindungen der allgemeinen Formel (X) mit einem geeigneten Diazotierungsreagenz, bevorzugt Natriumnitrit in saurem Milieu, die Verbindungen der allgemeinen Formel (XI) erhalten werden. Bei Einsatz enantiomerenreiner Verbindungen werden die entsprechenden enantiomerenreinen Hydroxycarbonsäureverbindungen erhalten, wobei die Reaktion unter Retention der Konfiguration abläuft.

Ein weiterer Zugang zu Verbindungen der allgemeinen Formel (XI), in der die Reste A wie eingangs erwähnt definiert sind, besteht in der Alkylierung der Verbindung



mit entsprechend substituierten Benzylchloriden, Benzylbromiden oder Benzyljodiden der allgemeinen Formel

5



in der A wie eingangs erwähnt definiert ist und X ein Chlor-, Brom- oder Jodatom bedeutet, in Analogie zu literaturbekannten Methoden (Michael T. Crimmins, Kyle A. Emmitte und Jason D. Katz, Org. Lett. 2, 2165-2167 [2000]).

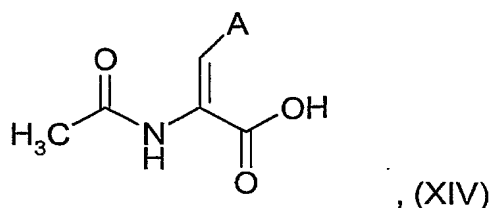
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Die entstehenden diastereomeren Produkte können dann mit Hilfe physikochemischer Methoden, bevorzugt mit Hilfe chromatographischer Methoden, getrennt werden. Die hydrolytische Abspaltung des chiralen Auxiliars, Kupplung mit Aminen der allgemeinen Formel  $\text{HNR}^2\text{R}^3$  und Abspaltung der Benzylschutzgruppe eröffnet ebenfalls einen Zugang zu enantiomerenreinen Hydroxycarbonsäureverbindungen des allgemeinen Formel (V).

5

Verbindungen der allgemeinen Formel (XI), in der die Reste A wie eingangs erwähnt definiert sind, können weiterhin durch Verkochen von 2-Acetylamino-3-phenylacrylsäuren der allgemeinen Formel

10



mittels starker Säuren und anschließender Reduktion der entstandenen 2-Hydroxy-3-phenyl-acrylsäuren erhalten werden.

5

Die Ausgangsverbindungen der allgemeinen Formel (VI) erhält man beispielsweise durch Umsetzung von Aminen der allgemeinen Formel  $\text{HNR}^2\text{R}^3$  mit 2-(Alkoxy-carbonylmethyl)-3-aryl-propansäuren und anschließende hydrolytische Abspaltung der Alkylgruppe. Die erforderlichen 2-(Alkoxy-carbonylmethyl)-3-aryl-propansäuren können in Analogie zu literaturbekannten Methoden (David A. Evans, Leester D. Wu, John J. M. Wiener, Jeffrey S. Johnson, David H. B. Ripin und Jason S. Tedrow, J. Org.Chem 64, 6411-6417 [1999]; Saul G. Cohen und Aleksander Milovanovic, J. Am. Chem. Soc. 90, 3495-3502 [1968]; Hiroyuki Kawano, Youichi Ishii, Takao Ikariya, Masahiko Saburi, Sadao Yoshikawa, Yasuzo Uchida und Hidenori Kumobayashi, Tetrahedron Letters 28, 1905-1908 [1987]) hergestellt werden. Carbonsäuren der allgemeinen Formel (VIII) können nach den in der WO 98/11128 angegebenen Verfahren aus allgemein zugänglichen Ausgangsmaterialien hergestellt werden.

Die erhaltenen Verbindungen der allgemeinen Formel (I) können, sofern sie geeignete basische Funktionen enthalten, insbesondere für pharmazeutische Anwendungen in ihre physiologisch verträglichen Salze mit anorganischen oder organischen Säuren übergeführt werden. Als Säuren kommen hierfür beispielsweise Salzsäure, Bromwasserstoffsäure, Phosphorsäure, Salpetersäure, Schwefelsäure, Methansulfonsäure, Ethansulfonsäure, Benzoisulfonsäure, *p*-Toluolsulfonsäure, Essigsäure, Fumarsäure, Bernsteinsäure, Milchsäure, Mandelsäure, Äpfelsäure, Zitronensäure, Weinsäure oder Maleinsäure in Betracht.

Die vorliegende Erfindung betrifft Racemate, sofern die Verbindungen der allgemeinen Formel (I) nur ein Chiralitätselement besitzen. Die Anmeldung umfasst jedoch auch die einzelnen diastereomeren Antipodenpaare oder deren Gemische,

die dann vorliegen, wenn mehr als ein Chiralitätselement in den Verbindungen der allgemeinen Formel (I) vorhanden ist, sowie die einzelnen optisch aktiven Enantiomeren, aus denen sich die erwähnten Racemate zusammensetzen.

- 5 Ebenfalls mit vom Gegenstand dieser Erfindung umfasst sind die erfindungsgemäßen Verbindungen, einschließlich deren Salze, in denen ein oder mehrere Wasserstoffatome durch Deuterium ausgetauscht sind.

Die neuen Verbindungen der allgemeinen Formel (I) und deren physiologisch  
0 verträgliche Salze weisen wertvolle pharmakologische Eigenschaften auf, die auf ihre selektiven CGRP-antagonistischen Eigenschaften zurückgehen. Ein weiterer Gegenstand der Erfindung sind diese Verbindungen enthaltende Arzneimittel, deren Verwendung und deren Herstellung.

- 5 Die voranstehend genannten neuen Verbindungen und deren physiologisch verträgliche Salze besitzen CGRP-antagonistische Eigenschaften und zeigen gute Affinitäten in CGRP-Rezeptorbindungsstudien. Die Verbindungen weisen in den nachstehend beschriebenen pharmakologischen Testsystemen CGRP-antagonistische Eigenschaften auf.

0 Zum Nachweis der Affinität der voranstehend genannten Verbindungen zu humanen CGRP-Rezeptoren und ihrer antagonistischen Eigenschaften wurden die folgenden Versuche durchgeführt:

- 15 A. Bindungsstudien mit (den humanen CGRP-Rezeptor exprimierenden) SK-N-MC-Zellen

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SK-N-MC-Zellen werden in "Dulbecco's modified Eagle Medium" kultiviert. Das Medium konfluenter Kulturen wird entfernt. Die Zellen werden zweimal mit PBS-  
30 Puffer (Gibco 041-04190 M) gewaschen, durch Zugabe von PBS-Puffer, versetzt mit 0.02% EDTA, abgelöst und durch Zentrifugation isoliert. Nach Resuspension in 20 ml "Balanced Salts Solution" [BSS (in mM): NaCl 120, KCl 5.4, NaHCO<sub>3</sub> 16.2, MgSO<sub>4</sub> 0.8, NaHPO<sub>4</sub> 1.0, CaCl<sub>2</sub> 1.8, D-Glucose 5.5, HEPES 30, pH 7.40] werden die Zellen

zweimal bei 100 x g zentrifugiert und in BSS resuspendiert. Nach Bestimmung der Zellzahl werden die Zellen mit Hilfe eines Ultra-Turrax homogenisiert und für 10 Minuten bei 3000 x g zentrifugiert. Der Überstand wird verworfen und das Pellet in Tris-Puffer (10 mM Tris, 50 mM NaCl, 5 mM MgCl<sub>2</sub>, 1 mM EDTA, pH 7.40), angereichert mit 1% Rinderserum-Albumin und 0.1% Bacitracin, rezentrifugiert und resuspendiert (1 ml / 1000000 Zellen). Das Homogenat wird bei -80°C eingefroren. Die Membranpräparationen sind bei diesen Bedingungen für mehr als 6 Wochen stabil.

- 3) Nach Auftauen wird das Homogenat 1:10 mit Assay-Puffer (50 mM Tris, 150 mM NaCl, 5 mM MgCl<sub>2</sub>, 1 mM EDTA, pH 7.40) verdünnt und 30 Sekunden lang mit einem Ultra-Turrax homogenisiert. 230 µl des Homogenats werden für 180 Minuten bei Raumtemperatur mit 50 pM <sup>125</sup>I-Iodotyrosyl-Calcitonin-Gen-Related Peptide (Amersham) und ansteigenden Konzentrationen der Testsubstanzen in einem Gesamtvolumen von 250 µl inkubiert. Die Inkubation wird durch rasche Filtration durch mit Polyethylenimin (0.1%) behandelte GF/B-Glasfaserfilter mittels eines Zellharvesters beendet. Die an Protein gebundene Radioaktivität wird mit Hilfe eines Gammacounters bestimmt. Als nichtspezifische Bindung wird die gebundene Radioaktivität nach Gegenwart von 1 µM humanem CGRP-alpha während der Inkubation definiert.

Die Analyse der Konzentrations-Bindungskurven erfolgt mit Hilfe einer computergestützten nichtlinearen Kurvenanpassung.

- 5 Die eingangs erwähnten Verbindungen zeigen in dem beschriebenen Test IC<sub>50</sub>-Werte ≤ 10000 nM.

#### B. CGRP-Antagonismus in SK-N-MC-Zellen

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- 0 SK-N-MC-Zellen (1 Mio. Zellen) werden zweimal mit 250 µl Inkubationspuffer (Hanks' HEPES, 1 mM 3-Isobutyl-1-methylxanthin, 1% BSA, pH 7.4) gewaschen und bei 37°C für 15 Minuten vorinkubiert. Nach Zugabe von CGRP (10 µl) als Agonist in steigenden Konzentrationen (10<sup>-11</sup> bis 10<sup>-6</sup> M) bzw. zusätzlich von Substanz in 3 bis

4 verschiedenen Konzentrationen wird nochmals 15 Minuten inkubiert.

Intrazelluläres cAMP wird anschließend durch Zugabe von 20 µl 1M HCl und Zentrifugation (2000 x g, 4°C für 15 Minuten) extrahiert. Die Überstände werden in flüssigem Stickstoff eingefroren und bei -20°C gelagert.

Die cAMP-Gehalte der Proben werden mittels Radioimmunassay (Fa. Amersham) bestimmt und die pA<sub>2</sub>-Werte antagonistisch wirkender Substanzen graphisch ermittelt.

Die erfindungsgemäßen Verbindungen zeigen in dem beschriebenen *in vitro* Testmodell CGRP-antagonistische Eigenschaften in einem Dosisbereich zwischen 10<sup>-12</sup> bis 10<sup>-5</sup> M.

Aufgrund ihrer pharmakologischen Eigenschaften eignen sich die erfindungsgemäßen Verbindungen und deren Salze mit physiologisch verträglichen Säuren somit zur akuten und prophylaktischen Behandlung von Kopfschmerzen, insbesondere Migräne- bzw. Cluster-Kopfschmerz. Weiterhin beeinflussen die erfindungsgemäßen Verbindungen auch die folgenden Erkrankungen positiv:

Nicht-insulinabhängigen Diabetes mellitus ("NIDDM"), complex regional pain syndrome (CRPS1), cardiovaskuläre Erkrankungen, Morphintoleranz, Clostridiumtoxin-bedingte Durchfallerkrankungen, Erkrankungen der Haut, insbesondere thermische und strahlenbedingte Hautschäden inklusive Sonnenbrand, entzündliche Erkrankungen, z.B. entzündliche Gelenkerkrankungen (Arthritis), neurogene Entzündungen der oralen Mucosa, entzündliche Lungenerkrankungen, allergische Rhinitis, Asthma, Erkrankungen, die mit einer überschießenden Gefäßerweiterung und dadurch bedingter verringerter Gewebedurchblutung einhergehen, z.B. Schock und Sepsis. Darüber hinaus zeigen die erfindungsgemäßen Verbindungen eine lindernde Wirkung auf Schmerzzustände im allgemeinen.

Die Symptomatik menopausaler, durch Gefäßerweiterung und erhöhten Blutfluß verursachter Hitzewallungen östrogendefizienter Frauen sowie hormonbehandelter Prostatakarzinompatienten wird durch die CGRP-Antagonisten der vorliegenden Anwendung präventiv und akut-therapeutisch günstig beeinflusst, wobei sich dieser

Therapieansatz vor der Hormonsubstitution durch Nebenwirkungsarmut auszeichnet.

Die zur Erzielung einer entsprechenden Wirkung erforderliche Dosierung beträgt zweckmäßigerweise bei intravenöser oder subkutaner Gabe 0.01 bis 3 mg/kg Körpergewicht, vorzugsweise 0.01 bis 1 mg/kg Körpergewicht, bei oraler Gabe 0.01 bis 20 mg/kg Körpergewicht, vorzugsweise 0.1 bis 10 mg/kg Körpergewicht, und bei nasaler oder inhalativer Gabe 0.01 bis 10 mg/kg Körpergewicht, vorzugsweise 0.1 bis 10 mg/kg Körpergewicht, jeweils 1 bis 3 x täglich.

Sofern die Behandlung mit CGRP-Antagonisten oder/und CGRP-Release-Hemmern in Ergänzung zu einer üblichen Hormonsubstitution erfolgt, empfiehlt sich eine Verringerung der vorstehend angegebenen Dosierungen, wobei die Dosierung dann 1/5 der vorstehend angegebenen Untergrenzen bis zu 1/1 der vorstehend angegebenen Obergrenzen betragen kann.

Die erfindungsgemäß hergestellten Verbindungen können entweder alleine oder gegebenenfalls in Kombination mit anderen Wirksubstanzen zur Behandlung von Migräne intravenös, subkutan, intramuskulär, intrarektal, intranasal, durch Inhalation, transdermal oder oral erfolgen, wobei zur Inhalation insbesondere Aerosolformulierungen geeignet sind. Die Kombinationen können entweder simultan oder sequentiell verabreicht werden.

Als Kombinationspartner denkbare Wirkstoffklassen sind z.B. Angiotensin-II Rezeptorantagonisten,  $\alpha$ -Agonisten und  $\alpha$ -Antagonisten, 5-HT<sub>1B/1D</sub>-Agonisten, AMPA-Antagonisten, schwachen Analgetica, Antidepressiva, Antiemetika, Antikonvulsiva, Antimuscarinika,  $\beta$ -Blocker, Calcium-Antagonisten, Corticosteroide, Ergot-Alkaloiden, Histamin-H<sub>1</sub>-Rezeptorantagonisten, Neurokinin-Antagonisten, Neuroleptika, nichtsteroidale Antiphlogistika, NO-Synthase-Hemmer, Prokinetika, selektive Serotonin-Wiederaufnahme-Hemmer oder andere Antimigränemitteln, die zusammen mit einem oder mehreren inerten üblichen Trägerstoffen und/oder Verdünnungsmitteln, z.B. mit Maisstärke, Milchzucker, Rohrzucker, mikrokristalliner Zellulose, Magnesiumstearat, Polyvinylpyrrolidon, Zitronensäure, Weinsäure, Wasser, Wasser/Ethanol, Wasser/Glycerin, Wasser/Sorbit, Wasser/Polyethylen-

glykol, Propylenglykol, Cetylstearylalkohol, Carboxymethylcellulose oder fetthaltigen Substanzen wie Hartfett oder deren geeigneten Gemischen, in übliche galenische Zubereitungen wie Tabletten, Dragées, Kapseln, Pulver, Suspensionen, Lösungen, Dosieraerosole oder Zäpfchen eingearbeitet werden können.

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Für die oben erwähnten Kombinationen kommen somit als weitere Wirksubstanzen beispielsweise die nicht-steroidalen Antiphlogistika Aceclofenac, Acemetacin, Acetylsalicylsäure, Azathioprin, Diclofenac, Diflunisal, Fenbufen, Fenoprofen, Flurbiprofen, Ibuprofen, Indometacin, Ketoprofen, Leflunomid, Lornoxicam, Mefenaminsäure, Naproxen, Phenylbutazon, Piroxicam, Sulfasalazin, Tenoxicam, Zomepirac oder deren physiologisch verträgliche Salze sowie Meloxicam und andere selektive COX2-Inhibitoren, wie beispielsweise Rofecoxib und Celecoxib, in Betracht.

0

Weiterhin können z.B. Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Tasosartan, Telmisartan, Valsartan, Duloxetine, Ergotamin, Dihydroergotamin, Metoclopramid, Domperidon, Diphenhydramin, Cyclizin, Promethazin, Chlorpromazin, Vigabatrin, Timolol, Isomethepten, Pizotifen, Botox, Gabapentin, Topiramid, Riboflavin, Montelukast, Lisinopril, Prochlorperazin, Dexamethason, Flunarizin, Dextropropoxyphen, Meperidin, Metoprolol, Propranolol, Nadolol, Atenolol, Clonidin, Indoramin, Carbamazepin, Phenytoin, Valproat, Amitriptylin, Lidocain oder Diltiazem und andere 5-HT<sub>1B/1D</sub>-Agonisten wie z.B. Almotriptan, Avitriptan, Donitriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan und Zolmitriptan sowie deren physiologisch verträgliche Salze verwendet werden.

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Die Dosis für diese Wirksubstanzen beträgt hierbei zweckmäßigerweise 1/5 der üblicherweise empfohlenen niedrigsten Dosierung bis zu 1/1 der normalerweise empfohlenen Dosierung, also beispielsweise 20 bis 100 mg Sumatriptan.

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Ein weiterer Gegenstand der Erfindung ist die Verwendung der erfindungsgemäßen Verbindungen als wertvolle Hilfsmittel zur Erzeugung und Reinigung (Affinitätschromatographie) von Antikörpern sowie, nach geeigneter radioaktiver Markierung, beispielsweise durch Tritiumierung geeigneter Vorstufen, beispielsweise durch katalytische Hydrierung mit Tritium oder Ersatz von Halogenatomen durch Tritium,

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in RIA- und ELISA-Assays und als diagnostische bzw. analytische Hilfsmittel in der Neurotransmitter-Forschung.

## Experimenteller Teil

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Für die hergestellten Verbindungen liegen in der Regel IR-,  $^1\text{H}$ -NMR und/oder Massenspektren vor.

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Wenn nicht anders angegeben, werden  $R_f$ -Werte unter Verwendung von DC-Fertigplatten Kieselgel 60 F254 (E. Merck, Darmstadt, Artikel-Nr. 1.05714) ohne Kammer-sättigung bestimmt. Die bei den Fließmitteln angegebenen Verhältnisse beziehen sich auf Volumeneinheiten der jeweiligen Lösungsmittel. Die angegebenen Volumeneinheiten bei  $\text{NH}_3$  beziehen sich auf eine konzentrierte Lösung von  $\text{NH}_3$  in Wasser.

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Soweit nicht anders vermerkt sind die bei den Aufarbeitungen der Reaktionslösungen verwendeten Säure-, Basen- und Salzlösungen wässrige Systeme der angegebenen Konzentrationen.

Zu chromatographischen Reinigungen wird Kieselgel der Firma Millipore (MATREX<sup>TM</sup>, 35 bis 70  $\mu\text{m}$ ) verwendet.

Die angegebenen HPLC-Daten werden unter nachstehend angeführten Parametern gemessen:

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### Methode A:

Analytische Säule: Zorbax-Säule (Agilent Technologies), SB (Stable Bond) C18; 3.5  $\mu\text{m}$ ; 4.6 x 75 mm; Säulentemperatur: 30°C; Fluss: 0.8 mL / min; Injektionsvolumen: 5  $\mu\text{L}$ ; Detektion bei 254 nm

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Zeit (min)	Volumenprozent Wasser (mit 0.1% Ameisensäure)	Volumenprozent Acetonitril (mit 0.1% Ameisensäure)
0	95	5
9	10	90
10	10	90
11	95	5

Bei präparativen HPLC-Reinigungen werden in der Regel die gleichen Gradienten verwendet, die bei der Erhebung der analytischen HPLC-Daten benutzt wurden. Die

Sammlung der Produkte erfolgt massengesteuert, die Produkt enthaltenden Fraktionen werden vereinigt und gefriergetrocknet.

Falls nähere Angaben zur Konfiguration fehlen, bleibt offen, ob es sich um reine Enantiomere handelt oder ob partielle oder gar völlige Racemisierung eingetreten ist.

5

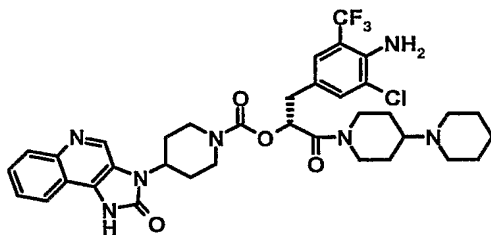
In den Versuchsbeschreibungen werden die folgenden Abkürzungen verwendet:

DCM	Dichlormethan
DMAP	4-Dimethylaminopyridin
0 DMF	<i>N,N</i> -Dimethylformamid
EtOAc	Essigsäureethylester
HCl	Salzsäure
LiOH	Lithiumhydroxid
MeOH	Methanol
5 RT	Raumtemperatur
TBTU	2-(1 <i>H</i> -Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-Tetrafluorborat
THF	Tetrahydrofuran

### Beispiel 1

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4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester



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(1a) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester

Zu der Mischung aus 0.79 g (6.42 mmol) DMAP und 100 mL Pyridin wurden 1.29 g (6.42 mmol) 4-Chlorameisensäure-4-nitrophenylester zugegeben und 1 h bei RT

gerührt. Danach wurde eine Lösung von 2.0 g (6.42 mmol) (R)-3-(4-Amino-3-chlor-5-trifluormethyl-phenyl)-2-hydroxy-propionsäureethylester in 15 mL Pyridin unter Rühren bei RT zugetropft und weitere 2 h bei RT gerührt. Anschließend wurde die Mischung mit 1.72 g (6.42 mmol) 3-Piperidin-4-yl-1,3-dihydro-imidazo[4,5-c]chinolin-2-on versetzt und 2 Tage bei RT gerührt. Das Reaktionsgemisch wurde unter vermindertem Druck eingeeengt, mit 200 mL EtOAc und 200 mL 15% K<sub>2</sub>CO<sub>3</sub>-Lösung versetzt, die organische Phase abgetrennt, getrocknet und eingeeengt. Der Rückstand wurde säulenchromatographisch (Kieselgel, Gradient DCM zu DCM/MeOH/NH<sub>3</sub> 0:95:5) gereinigt.

Ausbeute: 1.2 g (31% der Theorie)

ESI-MS: (M+H)<sup>+</sup> = 606/608 (CI)

Retentionszeit (HPLC): 6.7 min (Methode A)

(1b) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester

1.20 g (1.98 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester, gelöst in 30 mL THF, wurde bei RT mit einer Lösung von 74 mg (3.0 mmol) LiOH in 30 mL Wasser versetzt und 3 h bei RT gerührt. Das Reaktionsgemisch wurde unter vermindertem Druck eingeeengt, der Rückstand mit 100 mL Wasser versetzt und mit 1 M HCl angesäuert. Der Niederschlag wurde abgesaugt, mit 50 mL Wasser gewaschen und im Umlufttrockenschrank getrocknet.

Ausbeute: 0.88 g (77% der Theorie)

ESI-MS: (M+H)<sup>+</sup> = 578/580 (CI)

Retentionszeit (HPLC): 5.8 min (Methode A)

(1c) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester

Eine Mischung aus 80 mg (0.138 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(R)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester, 23.6 mg (0.14 mmol) [1,4']Bipiperidiny, 46.6 mg (0.14 mmol) TBTU, 0.041 mL (0.28 mmol) Triethylamin und 1.8 mL DMF wurde über Nacht bei RT

gerührt. Das Reaktionsgemisch wurde direkt mittels HPLC-MS (Säule: Agilent Zorbax Stable Bond RP C18, 5  $\mu$ M, 30x100 mm; Fluss 30 mL/min; Gradient: Wasser/Acetonitril) und anschließender Lyophilisation aufgereinigt.

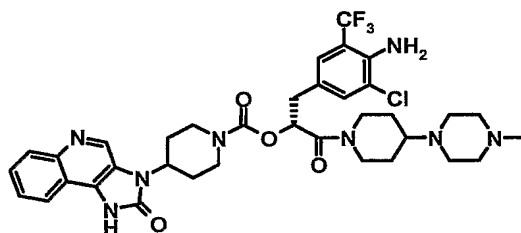
Ausbeute: 77 mg (76% der Theorie)

5 ESI-MS:  $(M+H)^+ = 728/730$  (Cl)

Retentionszeit (HPLC): 4.8 min (Methode A)

### Beispiel 2

0 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester



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Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluor-methyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-4-piperidin-4-yl-piperazin das Produkt erhalten.

0 Ausbeute: 76 mg (74% der Theorie)

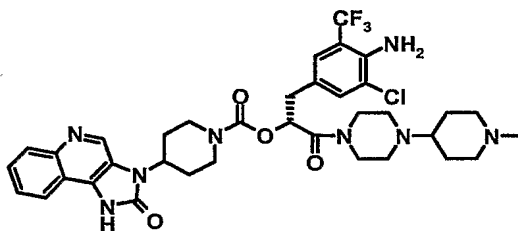
ESI-MS:  $(M+H)^+ = 743/745$  (Cl)

Retentionszeit (HPLC): 5.5 min (Methode A)

### Beispiel 3

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4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 26 mg (0.14 mmol) 1-(1-Methyl-piperidin-4-yl)-piperazin das Produkt erhalten.

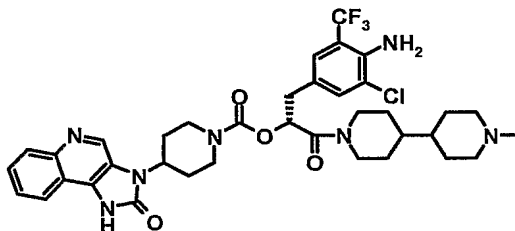
Ausbeute: 68 mg (66% der Theorie)

ESI-MS: (M+H)<sup>+</sup> = 743/745 (Cl)

Retentionszeit (HPLC): 4.0 min (Methode A)

#### Beispiel 4

4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethyl ester



Analog Beispiel (1c) wurden aus 80 mg (0.14 mmol) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluor-methyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-[4,4']bipiperidiny das Produkt erhalten.

Ausbeute: 73 mg (71% der Theorie)

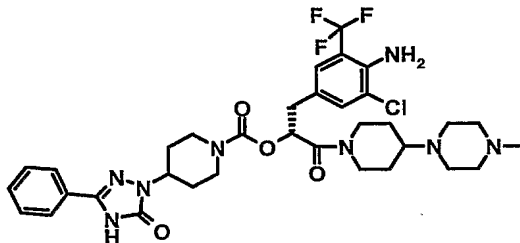
ESI-MS: (M+H)<sup>+</sup> = 742/744 (Cl)

Retentionszeit (HPLC): 4.9 min (Methode A)

Beispiel 5

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester

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(5a) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester

Analog Beispiel (1a) wurden aus 2.0 g (6.42 mmol) (*R*)-3-(4-Amino-3-chlor-5-trifluormethyl-phenyl)-2-hydroxy-propionsäureethylester und 2.41 g (65%, 6.42 mmol) 5-Phenyl-2-piperidin-4-yl-2,4-dihydro-1,2,4-triazol-3-on das Produkt erhalten werden.

Ausbeute: 1.0 g (27% der Theorie)

ESI-MS:  $(M+H)^+ = 582/584$  (CI)

Retentionszeit (HPLC): 8.9 min (Methode A)

(5b) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester

Analog Beispiel (1b) wurden aus 1.0 g (1.72 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-ethoxycarbonyl-ethylester und 64 mg (2.60 mmol) LiOH das Produkt erhalten werden.

Ausbeute: 0.91 g (96% der Theorie)

ESI-MS:  $(M+H)^+ = 554/556$  (CI)

Retentionszeit (HPLC): 7.5 min (Methode A)

(5c) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester

Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-4-piperidin-4-yl-piperazin das Produkt erhalten.

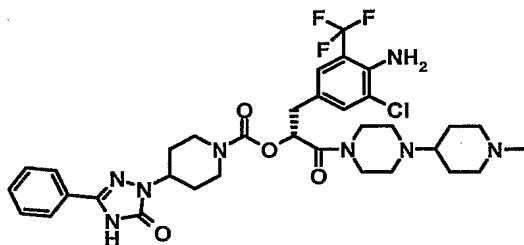
Ausbeute: 84 mg (84% der Theorie)

ESI-MS:  $(M+H)^+ = 719/721$  (Cl)

Retentionszeit (HPLC): 5.4 min (Methode A)

#### Beispiel 6

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 26 mg (0.14 mmol) 1-(1-Methyl-piperidin-4-yl)-piperazin das Produkt erhalten.

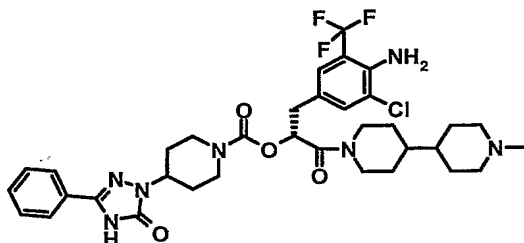
Ausbeute: 84 mg (84% der Theorie)

ESI-MS:  $(M+H)^+ = 719/721$  (Cl)

Retentionszeit (HPLC): 5.0 min (Methode A)

#### Beispiel 7

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethyl ester



Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 25 mg (0.14 mmol) 1-Methyl-[4,4']bipiperidiny-1 das

Produkt erhalten.

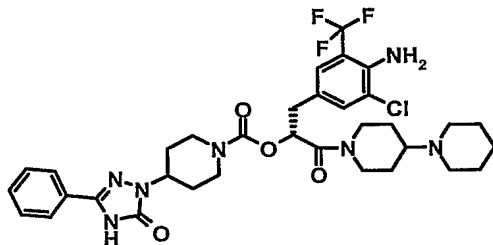
Ausbeute: 76 mg (76% der Theorie)

ESI-MS:  $(M+H)^+ = 718/720$  (Cl)

Retentionszeit (HPLC): 6.0 min (Methode A)

#### Beispiel 8

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester

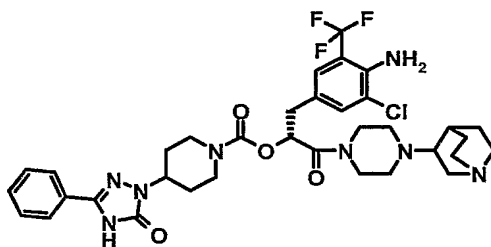


Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 24 mg (0.14 mmol) [1,4']Bipiperidiny-1 das Produkt erhalten.

Ausbeute: 71 mg (73% der Theorie)  
 ESI-MS:  $(M+H)^+ = 704/706$  (CI)  
 Retentionszeit (HPLC): 6.0 min (Methode A)

## 5 Beispiel 9

4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester



Analog Beispiel (1c) wurden aus 77 mg (0.14 mmol) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-2-(4-amino-3-chlor-5-trifluormethyl-phenyl)-1-carboxy-ethylester und 27 mg (0.14 mmol) 3-Piperazin-1-yl-1-aza-bicyclo[2.2.2]octan das Produkt erhalten.

Ausbeute: 13 mg (13% der Theorie)  
 ESI-MS:  $(M+H)^+ = 731/733$  (CI)  
 Retentionszeit (HPLC): 5.6 min (Methode A)

Die nachfolgenden Beispiele beschreiben die Herstellung pharmazeutischer Anwendungsformen, die als Wirkstoff eine beliebige Verbindung der allgemeinen Formel (I) enthalten:

## 5 Beispiel I:

Kapseln zur Pulverinhalation mit 1 mg Wirkstoff

Zusammensetzung:

1 Kapsel zur Pulverinhalation enthält:

Wirkstoff	1.0 mg
Milchzucker	20.0 mg
Hartgelatinekapseln	<u>50.0 mg</u>
5	71.0 mg

Herstellungsverfahren:

Der Wirkstoff wird auf die für Inhalativa erforderliche Korngröße gemahlen. Der gemahlene Wirkstoff wird mit dem Milchzucker homogen gemischt. Die Mischung  
0 wird in Hartgelatinekapseln abgefüllt.

Beispiel II:

Inhalationslösung für Respimat® mit 1 mg Wirkstoff

5

Zusammensetzung:

1 Hub enthält:

Wirkstoff	1.0	mg
Benzalkoniumchlorid	0.002	mg
10 Dinatriumedetat	0.0075	mg
Wasser gereinigt ad	15.0	µl

Herstellungsverfahren:

15 Der Wirkstoff und Benzalkoniumchlorid werden in Wasser gelöst und in Respimat®-Kartuschen abgefüllt.

Beispiel III:

30 Inhalationslösung für Vernebler mit 1 mg Wirkstoff

Zusammensetzung:

1 Fläschchen enthält:

Wirkstoff	0.1	g
Natriumchlorid	0.18	g
Benzalkoniumchlorid	0.002	g
Wasser gereinigt ad	20.0	ml

5

Herstellungsverfahren:

Wirkstoff, Natriumchlorid und Benzalkoniumchlorid werden in Wasser gelöst.

Beispiel IV:

10

Treibgas-Dosieraerosol mit 1 mg Wirkstoff

Zusammensetzung:

1 Hub enthält:

5	Wirkstoff	1.0	mg
	Lecithin	0.1	%
	Treibgas ad	50.0	µl

Herstellungsverfahren:

20 Der mikronisierte Wirkstoff wird in dem Gemisch aus Lecithin und Treibgas homogen suspendiert. Die Suspension wird in einen Druckbehälter mit Dosierventil abgefüllt.

Beispiel V:

25 Nasalspray mit 1 mg Wirkstoff

Zusammensetzung:

	Wirkstoff	1.0	mg
	Natriumchlorid	0.9	mg
30	Benzalkoniumchlorid	0.025	mg
	Dinatriumedetat	0.05	mg
	Wasser gereinigt ad	0.1	ml

Herstellungsverfahren:

Der Wirkstoff und die Hilfsstoffe werden in Wasser gelöst und in ein entsprechendes Behältnis abgefüllt.

5 Beispiel VI:

Injektionslösung mit 5 mg Wirksubstanz pro 5 ml

## Zusammensetzung:

0	Wirksubstanz	5 mg
	Glucose	250 mg
	Human-Serum-Albumin	10 mg
	Glykofurol	250 mg
	Wasser für Injektionszwecke ad	5 ml

5

Herstellung:

Glykofurol und Glucose in Wasser für Injektionszwecke auflösen (Wfl); Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; unter Stickstoff-Begasung in Ampullen abfüllen.

10

Beispiel VII:

Injektionslösung mit 100 mg Wirksubstanz pro 20 ml

## 15 Zusammensetzung:

	Wirksubstanz	100 mg
	Monokaliumdihydrogen- phosphat = $\text{KH}_2\text{PO}_4$	12 mg
	Dinatriumhydrogen- phosphat = $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$	2 mg
10	Natriumchlorid	180 mg
	Human-Serum-Albumin	50 mg
	Polysorbat 80	20 mg

Wasser für Injektionszwecke ad 20 ml

Herstellung:

Polysorbat 80, Natriumchlorid, Monokaliumdihydrogenphosphat und Dinatriumhydrogenphosphat in Wasser für Injektionszwecke (Wfl) auflösen; Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; in Ampullen abfüllen.

Beispiel VIII:

Lyophilisat mit 10 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz	10 mg
5 Mannit	300 mg
Human-Serum-Albumin	20 mg

Herstellung:

Mannit in Wasser für Injektionszwecke (Wfl) auflösen; Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; in Vials abfüllen; gefriertrocknen.

Lösungsmittel für Lyophilisat:

Polysorbat 80 = Tween 80	20 mg
5 Mannit	200 mg

Wasser für Injektionszwecke ad 10 ml

Herstellung:

Polysorbat 80 und Mannit in Wasser für Injektionszwecke (Wfl) auflösen; in Ampullen abfüllen.

Beispiel IX:

## Tabletten mit 20 mg Wirksubstanz

## Zusammensetzung:

	Wirksubstanz	20 mg
5	Lactose	120 mg
	Maisstärke	40 mg
	Magnesiumstearat	2 mg
	Povidon K 25	18 mg

3 Herstellung:

Wirksubstanz, Lactose und Maisstärke homogen mischen; mit einer wässrigen Lösung von Povidon granulieren; mit Magnesiumstearat mischen; auf einer Tablettenpresse abpressen; Tablettengewicht 200 mg.

5 Beispiel X:

## Kapseln mit 20 mg Wirksubstanz

## Zusammensetzung:

0	Wirksubstanz	20 mg
	Maisstärke	80 mg
	Kieselsäure. hochdispers	5 mg
	Magnesiumstearat	2.5 mg

5 Herstellung:

Wirksubstanz, Maisstärke und Kieselsäure homogen mischen; mit Magnesiumstearat mischen; Mischung auf einer Kapselfüllmaschine in Hartgelatine-Kapseln Grösse 3 abfüllen.

30 Beispiel XI:

## Zäpfchen mit 50 mg Wirksubstanz

Zusammensetzung:

Wirksubstanz 50 mg  
Hartfett (Adeps solidus) q.s. ad 1700 mg

5 Herstellung:

Hartfett bei ca. 38°C aufschmelzen; gemahlene Wirksubstanz im geschmolzenen Hartfett homogen dispergieren; nach Abkühlen auf ca. 35°C in vorgekühlte Formen ausgiessen.

0 Beispiel XII:

Injektionslösung mit 10 mg Wirksubstanz pro 1 ml

Zusammensetzung:

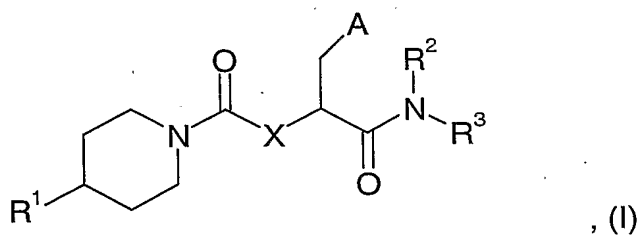
15 Wirksubstanz 10 mg  
Mannitol 50 mg  
Human-Serum-Albumin 10 mg  
Wasser für Injektionszwecke ad 1 ml

20 Herstellung:

Mannitol in Wasser für Injektionszwecke auflösen (Wfl); Human-Serum-Albumin zugeben; Wirkstoff unter Erwärmen auflösen; mit Wfl auf Ansatzvolumen auffüllen; unter Stickstoff-Begasung in Ampullen abfüllen.

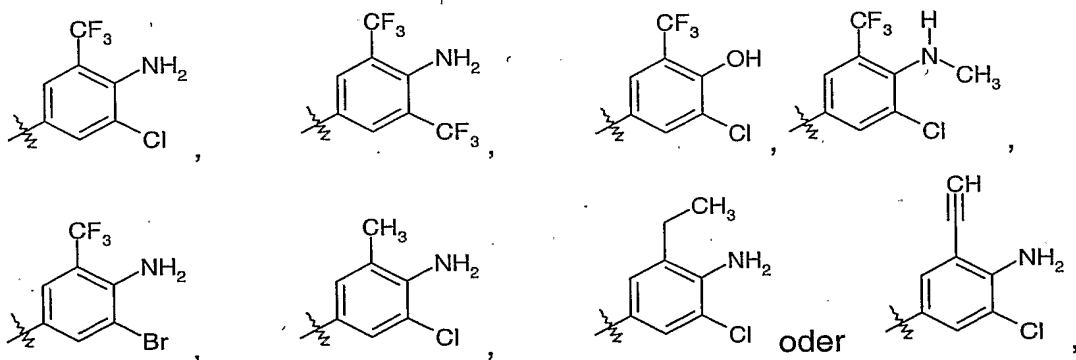
# Patentansprüche

## 1. CGRP-Antagonisten der allgemeinen Formel



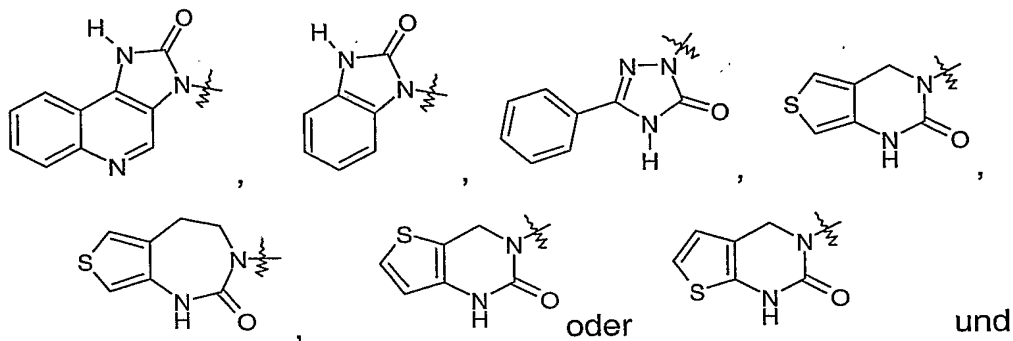
in der

## 0 A einen Rest der Formel



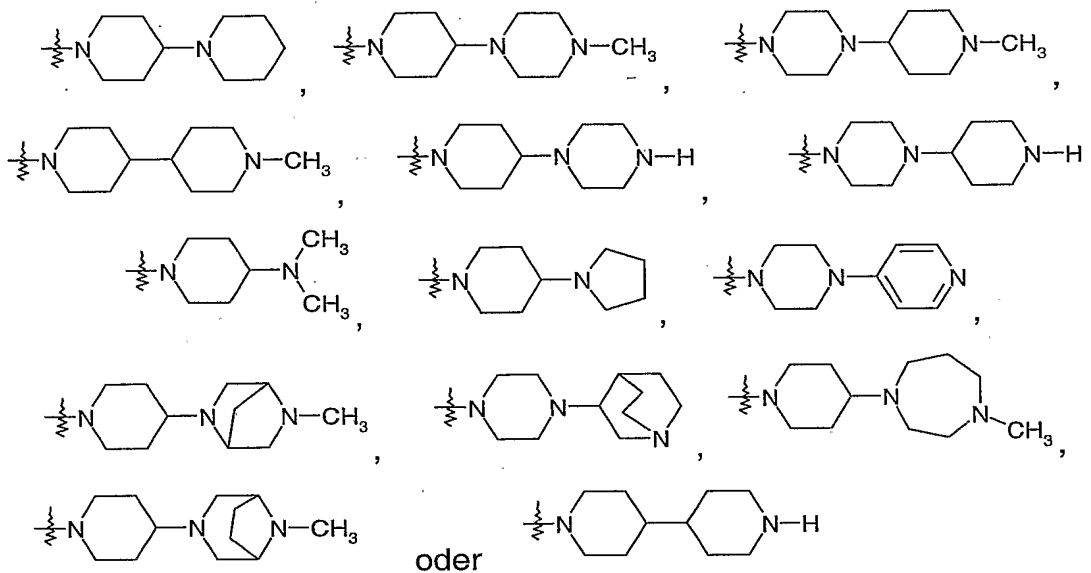
## 15 X ein Sauerstoffatom, eine Methylen- oder NH-Gruppe,

## R¹ einen Rest der Formel



-NR<sup>2</sup>R<sup>3</sup> einen Rest der Formel

5



10 bedeutet,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

15 2. Die Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1, die in der Tabelle der Beschreibung mit (1) bis (2353) fortlaufend nummeriert sind,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

20

3. Folgende Verbindungen der allgemeinen Formel (I) gemäß Anspruch 1:

(1) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-c]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester,

25

- (2) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,
- 5 (3) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,
- 10 (4) 4-(2-Oxo-1,2-dihydro-imidazo[4,5-*c*]chinolin-3-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethylester,
- 15 (5) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethylester,
- 20 (6) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure (*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethylester,
- (7) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-(1'-methyl-[4,4']bipiperidiny-1-yl)-2-oxo-ethylester,
- 25 (8) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[1,4']bipiperidiny-1'-yl-2-oxo-ethylester,
- 30 (9) 4-(5-Oxo-3-phenyl-4,5-dihydro-[1,2,4]triazol-1-yl)-piperidin-1-carbonsäure-(*R*)-1-(4-amino-3-chlor-5-trifluormethyl-benzyl)-2-[4-(1-aza-bicyclo[2.2.2]oct-3-yl)-piperazin-1-yl]-2-oxo-ethylester,

deren Tautomere, deren Diastereomere, deren Enantiomere, deren Hydrate, deren Gemische und deren Salze sowie die Hydrate der Salze.

4. Physiologisch verträgliche Salze der Verbindungen gemäß einem der Ansprüche 1 bis 3 mit anorganischen oder organischen Säuren.

5. Arzneimittel, enthaltend eine Verbindung gemäß einem der Ansprüche 1 bis 3 oder ein physiologisch verträgliches Salz gemäß Anspruch 4 neben gegebenenfalls einem oder mehreren inerten Trägerstoffen und/oder Verdünnungsmitteln.

6. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur akuten und prophylaktischen Behandlung von Kopfschmerzen, insbesondere Migräne- bzw. Cluster-Kopfschmerz.

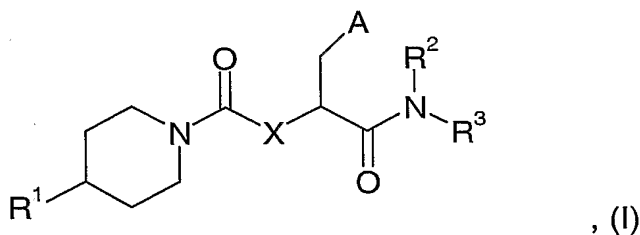
7. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur Bekämpfung von nicht-insulinabhängigem Diabetes-mellitus (NIDDM).

8. Verwendung einer Verbindung nach mindestens einem der Ansprüche 1 bis 4 zur Herstellung eines Arzneimittels zur Behandlung von CRPS1 (complex regional pain syndrome), von kardiovaskulären Erkrankungen, von Morphintoleranz, von Clostridiumtoxin-bedingten Durchfallerkrankungen, von Erkrankungen der Haut, insbesondere von thermischen und strahlungsbedingten Schäden inklusive Sonnenbrand, von entzündlichen Erkrankungen wie insbesondere entzündlicher Gelenkerkrankungen wie Arthritis, von neurogenen Entzündungen der oralen Mucosa, von entzündlichen Lungenerkrankungen, von allergischer Rhinitis, von Asthma, von Erkrankungen, die mit einer überschießenden Gefäßerweiterung und dadurch bedingter verringerter Gefäßdurchblutung, wie insbesondere Schock oder Sepsis, einhergeht, zur Linderung von Schmerzzuständen im allgemeinen oder zu präventiven oder akut therapeutischen Beeinflussung der durch Gefäßerweiterung und erhöhten Blutfluss verursachten Symptomatik von Hitzewallungen menopausaler, östrogendefizienter Frauen sowie hormonbehandelter Prostatakarzinompatienten.

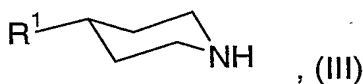
9. Verfahren zur Herstellung eines Arzneimittels gemäß Anspruch 5, dadurch gekennzeichnet, dass auf nichtchemischem Weg eine Verbindung nach mindestens einem der Ansprüche 1 bis 4 in einen oder mehrere inerte Trägerstoffe und/oder Verdünnungsmittel eingearbeitet wird.

10. Verfahren zur Herstellung der Verbindungen der allgemeinen Formel (I) nach mindestens einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass

(a) zur Herstellung von Verbindungen der allgemeinen Formel

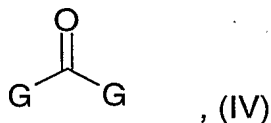


in der X das Sauerstoffatom oder die NH-Gruppe bedeutet und A und R¹ bis R³ wie in Anspruch 1 definiert sind, ein Piperidin der allgemeinen Formel



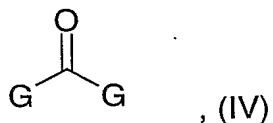
in der R¹ in Anspruch 1 definiert ist,

(i) mit einem Kohlensäurederivat der allgemeinen Formel



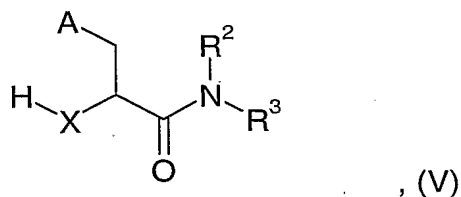
in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann, bedeutet, mit der Maßgabe, dass X die NH-Gruppe darstellt, oder

(ii) mit einem Kohlensäurederivat der allgemeinen Formel



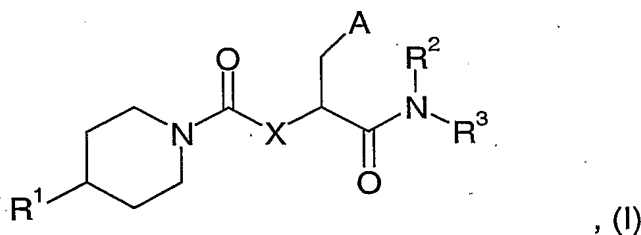
in der G eine nucleofuge Gruppe, die gleich oder verschieden sein kann,  
 5 bedeutet, mit der Maßgabe, dass X das Sauerstoffatom bedeutet,

und mit einer Verbindung der allgemeinen Formel

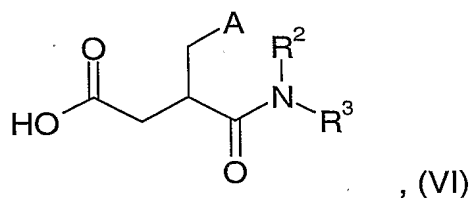


10 in der X das Sauerstoffatom oder eine –NH-Gruppe bedeutet und A, R<sup>2</sup> und R<sup>3</sup> wie in Anspruch 1 definiert sind, mit der Maßgabe, dass R<sup>2</sup> und R<sup>3</sup> keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, umgesetzt wird; oder

15 (b) zur Herstellung von Verbindungen der allgemeinen Formel

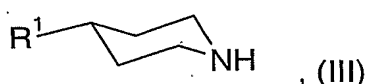


20 in der X die Methylengruppe bedeutet und A und R<sup>1</sup> bis R<sup>3</sup> wie in Anspruch 1 definiert sind, mit der Maßgabe, dass keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, eine Carbonsäure der allgemeinen Formel



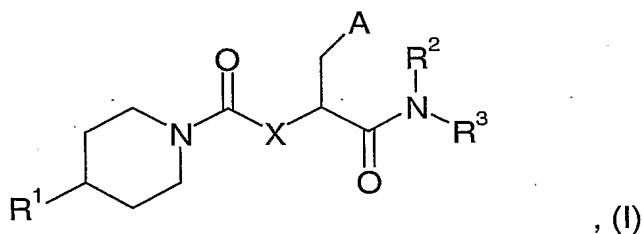
in der A, R<sup>2</sup> und R<sup>3</sup> wie in Anspruch 1 definiert sind, mit einem Piperidin der allgemeinen Formel

5

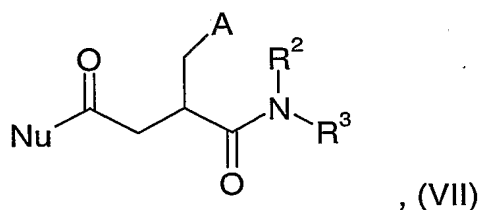


in der R<sup>1</sup> wie in Anspruch 1 definiert ist, gekuppelt wird; oder

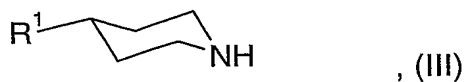
10 (c) zur Herstellung von Verbindungen der allgemeinen Formel



15 in der X die Methylengruppe bedeutet und A, R<sup>2</sup> und R<sup>3</sup> wie in Anspruch 1 definiert sind, mit der Maßgabe, dass diese Gruppen kein freies primäres oder sekundäres Amin enthalten, eine Verbindung der allgemeinen Formel



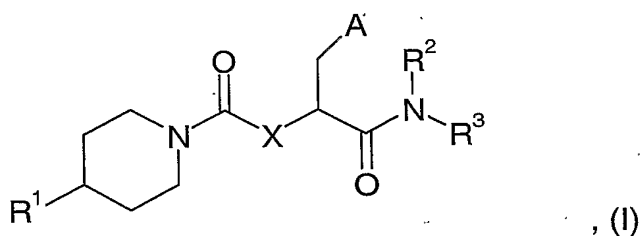
20 in der A, R<sup>2</sup> und R<sup>3</sup> wie in Anspruch 1 definiert sind, mit der Maßgabe, dass R<sup>2</sup> und R<sup>3</sup> kein freies primäres oder sekundäres Amin enthalten, und Nu eine Austrittsgruppe bedeutet, mit einem Piperidin der allgemeinen Formel



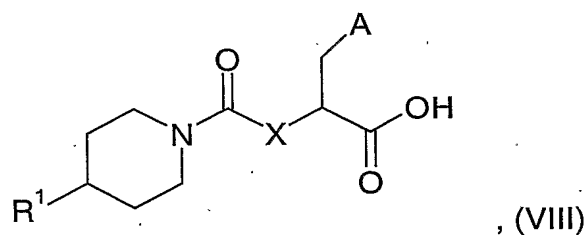
in der R¹ in Anspruch 1 definiert ist, gekuppelt wird; oder

5

(d) zur Herstellung von Verbindungen der allgemeinen Formel

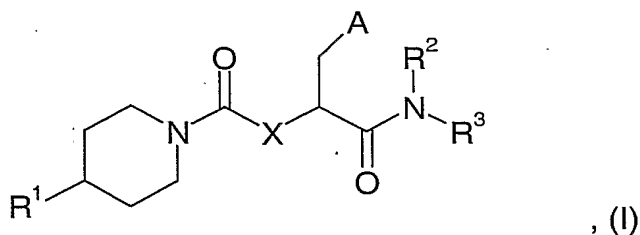


0 in der A, X und R¹ bis R³ wie in Anspruch 1 definiert sind, eine Carbonsäure der allgemeinen Formel

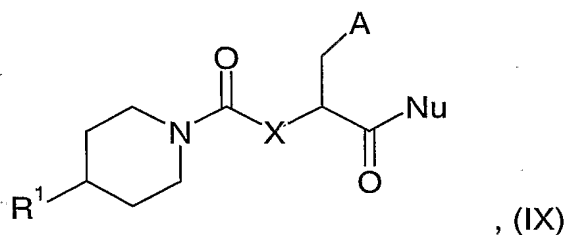


15 in der A, X und R¹ wie in Anspruch 1 definiert sind, mit einem Amin der allgemeinen Formel HNR²R³, in der R² und R³ wie in Anspruch 1 definiert sind, mit der Maßgabe, dass sie keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten, gekuppelt wird; oder

20 (e) zur Herstellung von Verbindungen der allgemeinen Formel



in der A, X und R<sup>1</sup> bis R<sup>3</sup> wie in Anspruch 1 definiert sind, mit der Maßgabe, dass  
kein freies primäres oder sekundäres Amin enthalten ist, eine Verbindung der  
5 allgemeinen Formel



in der A, X und R<sup>1</sup> wie in Anspruch 1 definiert sind und Nu eine Austrittsgruppe  
10 bedeutet, mit einem Amin der allgemeinen Formel HNR<sup>2</sup>R<sup>3</sup>, in der R<sup>2</sup> und R<sup>3</sup> wie in  
Anspruch 1 definiert sind, mit der Maßgabe, dass keine freie Carbonsäure- und/oder  
keine weitere freie primäre oder sekundäre aliphatische Aminofunktion enthalten ist,  
gekuppelt wird, und

15 erforderlichenfalls ein bei den vorstehend beschriebenen Umsetzungen verwendeter  
Schutzrest wieder abgespalten wird und/oder

gegebenenfalls verwendete Präcurserfunktionen in einer so erhaltenen Verbindung  
abgewandelt werden und/oder

20 gewünschtenfalls eine so erhaltene Verbindung der allgemeinen Formel (I) in ihre  
Stereoisomere aufgetrennt wird und/oder

eine so erhaltene Verbindung der allgemeinen Formel (I) in ihre Salze, insbesondere  
25 für die pharmazeutische Anwendung in ihre physiologisch verträglichen Salze  
übergeführt wird.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/003759

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D235/26 C07D249/12 C07D495/04 C07D401/14  
C07D487/08 C07D471/08 C07D451/04 C07D519/00 A61K31/437  
A61K31/4184 A61K31/4196 A61K31/519 A61K31/551 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, INSPEC, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MALLEE J J ET AL: "Receptor Activity-modifying Protein 1 Determines the Species Selectivity of Non-peptide CGRP Receptor Antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 277, no. 16, 19 April 2002 (2002-04-19), pages 14294-14298, XP002271313 ISSN: 0021-9258 the whole document	1-10
Y	US 6 344 449 B1 (RUDOLF KLAUS ET AL) 5 February 2002 (2002-02-05) the whole document	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents:

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 August 2005

Date of mailing of the international search report

19/08/2005

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Papathoma, S

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/003759

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/076432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18 September 2003 (2003-09-18) abstract; claims 1-17; examples 53-76 -----	1-10
Y	DE 102 27 294 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 8 January 2004 (2004-01-08) the whole document -----	1-10
P,X	DE 102 50 080 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 13 May 2004 (2004-05-13) abstract; claims 1-16; examples 17,19,21,22,24-27 -----	1-10

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Information on patent family members

International Application No

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# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP2005/003759

<b>A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES</b>					
IPK 7	C07D471/04	C07D235/26	C07D249/12	C07D495/04	C07D401/14
	C07D487/08	C07D471/08	C07D451/04	C07D519/00	A61K31/437
	A61K31/4184	A61K31/4196	A61K31/519	A61K31/551	A61P25/06
Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK					
<b>B. RECHERCHIERTE GEBIETE</b>					
Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole ) IPK 7 C07D A61K A61P					
Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen					
Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe) EPO-Internal, WPI Data, PAJ, BIOSIS, INSPEC, CHEM ABS Data					
<b>C. ALS WESENTLICH ANGESEHENE UNTERLAGEN</b>					
Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile				Betr. Anspruch Nr.
A	<p>MALLEE J J ET AL: "Receptor Activity-modifying Protein 1 Determines the Species Selectivity of Non-peptide CGRP Receptor Antagonists" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, Bd. 277, Nr. 16, 19. April 2002 (2002-04-19), Seiten 14294-14298, XP002271313 ISSN: 0021-9258 das ganze Dokument</p>				1-10
Y	<p>US 6 344 449 B1 (RUDOLF KLAUS ET AL) 5. Februar 2002 (2002-02-05) das ganze Dokument</p>				1-10
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<div style="display: flex; justify-content: space-between;"> <div> <input checked="" type="checkbox"/> Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen         </div> <div> <input checked="" type="checkbox"/> Siehe Anhang Patentfamilie         </div> </div>					
<p>° Besondere Kategorien von angegebenen Veröffentlichungen :</p> <p>"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist</p> <p>"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist</p> <p>"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)</p> <p>"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht</p> <p>"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist</p> <p>"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist</p> <p>"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden</p> <p>"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist</p> <p>"&amp;" Veröffentlichung, die Mitglied derselben Patentfamilie ist</p>					
Datum des Abschlusses der internationalen Recherche			Absendedatum des internationalen Recherchenberichts		
10. August 2005			19/08/2005		
Name und Postanschrift der Internationalen Recherchenbehörde Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Bevollmächtigter Bediensteter  Papathoma, S		

## C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
Y	WO 03/076432 A (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; HURNAUS, RUDOLF; RUDOLF, KL) 18. September 2003 (2003-09-18) Zusammenfassung; Ansprüche 1-17; Beispiele 53-76	1-10
Y	DE 102 27 294 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 8. Januar 2004 (2004-01-08) das ganze Dokument	1-10
P,X	DE 102 50 080 A1 (BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG) 13. Mai 2004 (2004-05-13) Zusammenfassung; Ansprüche 1-16; Beispiele 17,19,21,22,24-27	1-10

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Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen

PCT/EP2005/003759

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WO 03076432	A	18-09-2003	DE 10211770 A1 02-10-2003
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DE 10227294	A1	08-01-2004	AU 2003246414 A1 06-01-2004
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